Effects of N-Acetyl-L-Leucine on Ataxia-Telangiectasia (A-T): A multinational, multicenter, open-label, rater-blinded Phase II study

NCT Number: NCT03759678

Version and date of SAP: Updated final 2.0, 18 June 2024

STATISTICAL ANALYSIS PLAN

(Short) study title:	Effects of N-Acetyl-L-Leucine on Ataxia-Telangiectasia (A-T): A multinational, multicenter, open-label, rater-blinded Phase II study.
Name of the sponsor:	IntraBio Ltd.
Protocol identification:	IB1001-203, version 7.0 (Global version)/ version 7.1 (US version)
Version and date of SAP:	Updated final 2.0, 18 June 2024

VERSION HISTORY

Version	Date	History list
0.1	24 July 2019	Pre-final version for sponsor review.
1.0	17 October 2019	Final version
2.0	18 June 2024	Updated version, following protocol updates

APPROVAL PAGE

I hereby declare that I have read and reviewed this document. To the best of my knowledge, the content accurately states the intended analyses and output to be provided. This document is intended for an agreement on analysis and reporting details between the sponsor and [redacted].

(Lead) Statistician:
[redacted]

Signature Date

Sponsor representative:
[redacted].

Signature Date

Sponsor Biostatistician:
[redacted]

Signature Date

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LIST OF ABBREVIATIONS

_avg	Average
_recipr	Reciprocal
8MWT	8-Meter Walking Test
9HPT-D	9 Hole Peg Test of the Dominant Hand
9HPT-ND	9 Hole Peg Test of the Non-Dominant Hand
A-T	Ataxia-Telangiectasia
ADaM	Analysis Data Model
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Alanine Aminotransferase
ATC	Anatomic Therapeutic Chemical
BDRM	Blind Data Review Meeting
BL	Baseline
C-SSRS	Columbia-Suicide Severity Rating Scale
CFB	Change from Baseline
CGI-C	Clinical Global Impression of Change
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
CI	Confidence Interval
CI-CS	Clinical Impression of Change in Severity
CI-S	Clinical Impression of Severity
CRF	Case Report Form
EU	European Union
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
LoA	Limits of Agreement
LOCF	Last Observation Carried Forward
M(C)AR	Missing (Completely) at Random
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention-to-Treat
PI	Principal Investigator
PK	Pharmacokinetics
PM	Project Manager

PPS	Per Protocol Set
PT	Preferred Term
RBC	Red Blood Cell Count
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SARA	Scale for the Assessment and Rating of Ataxia
SCAFI	Spinocerebellar Ataxia Functional Index
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
US	United States
VAS	Visual Analogue Scale
WBC	White Blood Cell Count
WHO	World Health Organization

1 GENERAL

This Statistical Analysis Plan (SAP) describes in detail the methods and presentation of the data analyses which will be conducted by [redacted] for study IB1001-203. This plan is written in agreement with protocol version 7.0 (Global version), dated 05 October 2023/ US version 7.1 06 October 2023, and annotated Case Report Form (CRF), dated 26 July 2021, and the relevant Good Clinical Practice International Conference on Harmonisation (GCP-ICH) guidelines. Furthermore, sponsor requirements for reporting will be considered. Additional changes or updates of those documents or requirements may result in a new version of the reporting/statistical analysis plan. This plan is to be finalized preferably prior to enrolment of the first patient in the study, but at least before first programming/data analysis.

2 STUDY INFORMATION

2.1 Study Objectives

2.1.1 Parent Phase

Primary Objective

The primary objective of the Parent Phase is to evaluate the efficacy of N-Acetyl-L-Leucine based on blinded raters' clinical impression of change in severity (CI-CS) in the treatment of Ataxia-Telangiectasia (A-T).

Secondary Objectives

The secondary objectives of the Parent Phase are:

- To assess the clinical efficacy of N-Acetyl-L-Leucine on symptoms of ataxia, functioning, and quality of life for patients with A-T.
- To evaluate the safety and tolerability of N-Acetyl-L-Leucine at 4 g/day in patients with A-T, including patients aged ≥18 years in the United States and patients aged ≥13 years in Europe, and weight-tiered doses in patients 6 to 12 years of age in Europe.

Exploratory Objectives

The exploratory objective of the Parent Phase is:

- To characterize the pharmacokinetics (PK) of N-Acetyl-L-Leucine in patients with A-T.

2.1.2 Extension Phase

Primary Objective

The primary objective of the Extension Phase is to evaluate the efficacy of N-Acetyl-L-Leucine based on Scale for the Assessment and Rating of Ataxia (SARA) in the treatment of Ataxia-Telangiectasia (A-T).

Secondary Objectives

The secondary objective of the Extension Phase are:

- To evaluate the long-term safety and tolerability of N-Acetyl-L-Leucine at 4 g/day in patients aged ≥13 years, and weight-tiered doses in patients 6 to 12 years of age, with A-T
- To characterize the pharmacokinetics (PK) of N-Acetyl-L-Leucine in patients with A-T.

Exploratory Objectives

The exploratory objectives of the Extension Phase are:

- To assess the clinical efficacy of long-term treatment with N-Acetyl-L-Leucine on symptoms, functioning, and quality of life for patients with A-T
- To assess the effects of a 42-day (+14 days) washout from N-Acetyl-L-Leucine after one-year treatment on symptoms, functioning, and quality of life for patients with A-T

2.2 Design of the Study

2.2.1 Parent Phase

This is a multinational, multicenter, open-label, rater-blinded Phase II study investigating the efficacy and safety of N-Acetyl-L-Leucine for the treatment of A-T. Approximately 39 male and female patients aged ≥6 years in Europe or ≥18 years in the United States with a confirmed diagnosis of A-T are planned to be enrolled.

The visit schedule differs between “naïve” (patients not previously exposed to prohibited medications within the 6 weeks (42 days) before the initial screening visit) and “non-naïve” patients: see figures 1 and 2 below.

Figure 1: Study Scheme for Naïve Patients

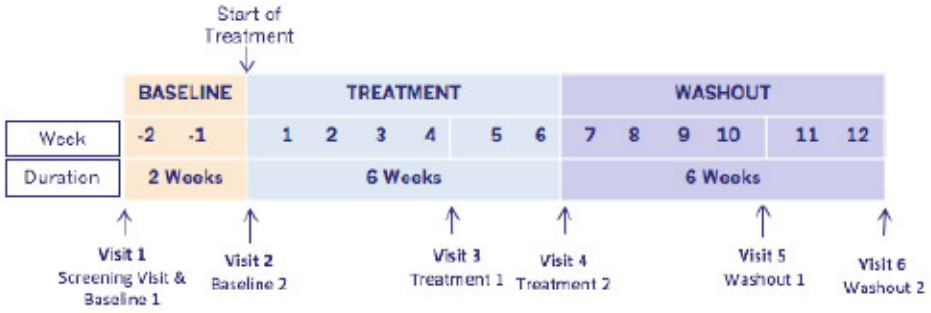
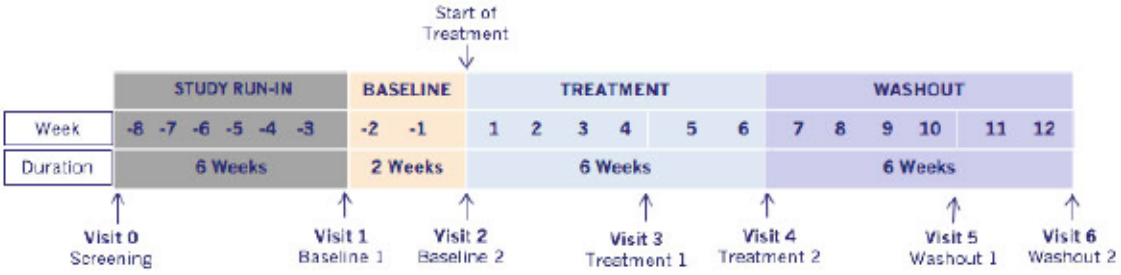


Figure 2: Study Scheme for Non-naïve Patients



2.2.2 Extension Phase

The (full) Extension phase is considered the study period starting with the Extension phase baseline (Visit 7) until Visit 12. In some instances, however, it may be beneficial to make the following split:

- Extension phase I is considered the study period starting with the Extension phase Visit 7 until Visit 10.
- Extension phase II is considered the study period starting with the Extension phase Visit 10 until Visit 12.

The Extension phase will enroll patients who have completed Visit 6 of the Parent study phase. Patients will receive treatment with IB1001 during the Extension Phase. phase. The Extension Phase is considered the study period starting with Visit 7 until Visit 12.

Patients will be assessed 6 times during the Extension Phase: at the start of the Extension Phase (Visit 7), after 6 months of treatment (Visit 8), after 1 year of treatment (Visit 9), after a 42-day (+14 day) post-extension-phase treatment washout (Visit 10), after 6 months of resuming treatment (Visit 11), and after 1 year of resuming treatment (Visit 12).

Baseline Visit of the Extension Phase

Visit 7 (Part A and B) is considered the baseline of the Extension Phase. The assessments (Part A and Part B) comprising Visit 7 may be conducted over a two-day period ("Part A" and "Part B"). If Visit 7B is scheduled 1 day (+6 days) after Visit 6

(Washout 2 of the Parent study), the assessments conducted at Visit 6 should count as Visit 7A (i.e. the assessments do not need to be repeated).

If Visit 7B cannot be scheduled 1 day (+6 days) after Visit 6, the assessments included in Visit 7A and Visit 7B should be performed over two consecutive days, i.e. Visit 7B occurs +1 day after Visit 7A.

In general Visit 7A will be the same as Visit 6 in the Parent phase, or within one week following Visit 6. But a non-seamless transition of several weeks or months is possible. The same subject numbers will be used throughout the Parent and the Extension study phase.

2.3 Study medication

2.3.1 Parent Phase

All patients are to receive N-Acetyl-L-Leucine (IB1001) in this single-arm study. The study drug will be taken during a 6-week (42 days + 7 days) treatment period. During the treatment phase of this study, the dosing of the study drug is as follows:

- Patients aged ≥13 years in Europe and aged ≥18 years in the United States will take 4 g per day: 2 g in the morning, 1 g in the afternoon, and 1 g in the evening.
- Patients aged 6-12 years weighing 15 to <25 kg will take 2 g per day: 1 g in the morning and 1 g in the evening.
- Patients aged 6-12 years weighing 25 to <35 kg will take 3 g per day: 1 g in the morning, 1 g in the afternoon, and 1 g in the evening.
- Patients aged 6-12 years weighing ≥35 kg will take 4 g per day: 2 g in the morning, 1g in the afternoon and 1 g in the evening (as per patients aged ≥13)

2.3.2 Extension Phase

All patients are to receive N-acetyl-L-leucine (IB1001) during the Extension Phase. The study drug will be taken for two 365-day (+/- 14 days) treatment periods. The patient's dose for the Extension Phase will be determined based on their age and weight at Visit 7, following the same tiered doses as for the Parent Phase (see Section 2.3.1).

In the event a patient turns 13 years old or a patient aged 6-12 years old changes weight categories between Visit 7 and Visit 8 of the Extension Phase, their daily dose will be adjusted accordingly at Visit 8. In the event a patient turns 13 years old or a patient aged 6-12 years old changes weight categories between Visit 8 and Visit 10, or Visit 10 and Visit 11 of the Extension Phase, their daily dose will be adjusted accordingly at Visit 10 or Visit 11.

2.4 Sample size

2.4.1 Parent Phase

It is postulated that N-Acetyl-L-Leucine will show effectiveness in 30% of patients and this success rate is viewed as being clinically important. Assume that this group of patients will have scores that are evenly distributed across the values 1 and 2 for the primary endpoint and further that the remaining 70% of patients will have scores that are evenly distributed between the values -1, 0, and 1. The resulting mean score is 0.45 and the standard deviation for the primary endpoint under these assumptions is then 1.02. With 30 patients reporting on the primary endpoint, the study will have 76% power to detect a treatment benefit in a 5% one-sided one-sample t-test.

Recruitment will continue until approximately 30 patients complete dosing. The following numbers of patients are foreseen:

- To be enrolled: Approximately 39 patients
- To be analyzed according to the modified Intention to Treat analysis (mITT): Approximately 36 patients
- To be analyzed according to the Per Protocol Set (PPS): Approximately 30 patients

2.4.2 Extension Phase

Sample size is determined by the number of patients that move into the Extension Phase. The expectation is that between 60% and 70% of patients will rollover. With 20 out of 32 patients (62.5%) rolling over, the study will have 80% power to detect an improvement in the success rate to 31% compared to the null hypothesis value of 10%.

2.5 Study flow chart

2.5.1 Parent Phase

Schedule of Events for "Naïve" Patients

Period	Baseline Period		Treatment Period		Wash-Out Period		Early Term.
Duration of the whole period	**1 Day**	**2 Weeks**	**6 Weeks**		**6 Weeks**		**1 Day**
Visit number	**Visit 1[1]**	**Visit 2[2]**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6 / EOS**	**ET**
Name of the Visit	**Screening/Bsl 1**	**Baseline 2**	**Treatment 1**	**Treatment 2**	**Washout 1**	**Washout 2**	**ET**
Timeline (Days)	*Day -14*	*Day 1, Start IMP*	*Day 28*	*Day 42*	*Day 70*	*Day 84*	*XX*
Visit Window allowed	*na*	*+7 days*	*+7 days*	*+7 days*	*+7 days*	*+ 7days*	*na*

Patient information and informed consent process	X						
Inclusion / exclusion criteria	X	X					
Patient weight and height measurements	X						
Confirmation prohibited medications have not been used in the past 42 days	X	X[3,4]					
Classify patient as "Naïve" or "Non-naïve"	X						
Patient demographics (in accordance with local regulations)	X						
Relevant medical history	X						
60-Day drug history	X						
Documentation of therapy	X	X	X	X	X	X	X
Physical examination	X			X		X	X
Vital signs	X	X	X	X	X	X	X
12-lead electrocardiogram (ECG)[5]	X		X		X		X
Urine test for N-Acetyl-D-Leucine[6]	X[7]	X			X	X	X
Blood safety laboratory tests[8]	X	X	X	X	X	X	X
Follicle stimulating hormone serum [8, 9]	X						
Urinalysis [8]	X	X	X	X	X	X	X
Urine by dipstick for pregnancy test[10]	X	X		X		X	X

Blood sample for sparse PK [6]	X	X	X	X	X	X	X
Quality of Life EQ-5D-5L for patients aged ≥18; EQ-5D-Y[11] for children aged <18 years	X	X	X	X	X	X	X
Scale for Ataxia Rating (SARA)	X	X	X	X	X	X	X
Scale for Spinocerebellar Ataxia Functional Index (SCAFI)[12]	X	X	X	X	X	X	X
Cognitive assessment according to standard procedures of the clinical site	X						
Determination of CI-CS Primary Anchor Test (9HPT-D or 8MWT)	X						
Clinical Global Impression of Severity (CGI-S) by Physician	X	X	X	X	X	X	X
Clinical Global Impression of Severity (CGI-S) by Caregiver	X	X	X	X	X	X	X
Clinical Global Impression of Severity (CGI-S) by Patient[13]	X	X	X	X	X	X	X
Clinical Global Impression of Change (CGI-C) by Physician				X		X	X
Clinical Global Impression of Change (CGI-C) by Caregiver				X		X	X
Clinical Global Impression of Change (CGI-C) by Patient[13]				X		X	X
Columbia-Suicide Severity Rating Scale	X	X	X	X	X	X	X
Documentation of concomitant medication[14]	X	X	X	X	X	X	X
Documentation of AEs	X	X	X	X	X	X	X

Dispensing of study drug		X	X[15]				
Intake of study drug at site		X[16]					
Return of study drug			X	X			X
Study drug compliance check			X[17]	X[18]			X[18]

[1] If the patient's eligibility is confirmed and their urine screen for N-Acetyl-D-Leucine is below the permitted threshold. The next visit, **Visit 2,** should be planned 14 days (+7 days) from **Visit 1.**

[2] All assessments must be done pre-dose

[3] At **Visit 2,** confirm no prohibited medications since **Visit 1**

[4] If the patient (or caregiver) states the patient has been using prohibited medication at **Visit 2,** they will be classified as non-compliant and withdrawn from the study

[5] If feasible, repeat assessments performed at treating physician's discretion if clinically significant results at **Visit 3**

[6] To be analyzed at PK lab

[7] If the patient's urine sample unexpectedly detects levels of N-Acetyl-D-Leucine above the permitted threshold, they will (provided eligible) switch to "non-naïve"

[8] To be analyzed at the central lab

[9] Only for post-menopausal women of non-child bearing potential with amenorrhea for at least 1 year prior to the first dose (and have not undergone sterilization procedures at least 6 months prior to the first dose)

[10] Only for women of childbearing potential; done at site

[11] In Europe only

[12] Two subtests, the 9-hole Peg Test of the Dominant Hand (9HPT-D) and 8-meter Walk Test (8MWT) will be videoed in a standardized format at every visit (except Visit 0).

[13] If the patient is able to provide the CGI-S/C

[14] Any concomitant medication needs to be recorded, used or not used for (symptoms of) A-T since the last 60 days prior to date of informed consent, up to End of Study / ET

[15] If needed

[16] Patient should not have used any of the prohibited concomitant medication 42 days prior to first dose of study drug, and have had a urine screen for N-Acetyl-D-Leucine below the permitted threshold prior to first dose of study drug.

[17] If Feasible

[18] Or after the Visit if IMP is returned via courier

Schedule of Events for "Non-naïve" Patients

	Study Run-In		Baseline Period		Treatment Period		Wash-Out Period		Early Term.
	Screening visit	Pre-treatment Washout							
Duration of the whole period	**1 Day**	**6 Weeks**	**2 Weeks**		**6 Weeks**		**6 Weeks**		**1 Day**
Visit number	**Visit 0**		**Visit 1[1]**	**Visit 2[2]**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6 / EOS**	**ET**
Name of the Visit	**Screening**		**Baseline 1**	**Baseline 2/ Start IMP**	**Treatment 1**	**Treatment 2**	**Washout 1**	**Washout 2**	**ET**
Timeline (Days)	*Day -56*		*Day -14*	*Day 1*	*Day 28*	*Day 42*	*Day 70*	*Day 84*	*na*
Visit Window allowed	*na*		*na*	*+7 days*	*+7 days*	*+7 days*	*+7 days*	*+7 days*	*na*
Patient information and informed consent process	X								
Inclusion / exclusion criteria	X		X	X					
Patient weight and height measurements	X								
Physical examination	X		X			X		X	X
Confirmation prohibited medications have not been used in the past 42 days at Visit 1/since Visit 1 for Visit 2			X	X[3]					
Confirmation prohibited medications have been used within past 42 days[4]	X								
Classify patient as "Naïve" or "Non-naïve"	X								
Patient demographics (in accordance with local regulations)	X								
Relevant medical history	X								
60-Day drug history	X								
Documentation of therapy	X		X	X	X	X	X	X	X
Vital signs	X		X	X	X	X	X	X	X
12-lead electrocardiogram (ECG)[5]			X		X		X		X

Urine Test for N-Acetyl-D-Leucine[6]			X[7]	X			X	X	X
Blood safety laboratory tests[8]			X	X	X	X	X	X	X
Follicle stimulating hormone serum[9]			X						
Urinalysis[8]			X	X	X	X	X	X	X
Urine by dipstick for pregnancy test[10]	X		X	X		X		X	X

Blood sample for sparse PK[6]			X	X	X	X	X	X	X
Quality of Life EQ-5D-5L for patients aged ≥18 years; EQ-5D-Y[11] for children aged <18 years			X	X	X	X	X	X	X
Scale for Ataxia Rating (SARA)	X		X	X	X	X	X	X	X
Scale for Spinocerebellar Ataxia Functional Index (SCAFI)[12]	X		X	X	X	X	X	X	X
Cognitive assessment according to standard procedures of the clinical site			X						
Determination of CI-CS Primary Anchor Test (9HPT-D or 8MWT)			X						
Clinical Global Impression of Severity (CGI-S) by Physician			X	X	X	X	X	X	X

Clinical Global Impression of Severity (CGI-S) by Caregiver			X	X	X	X	X	X	X
Clinical Global Impression of Severity (CGI-S) by Patient[13]			X	X	X	X	X	X	X
Clinical Global Impression of Change (CGI-C) by Physician						X		X	X
Clinical Global Impression of Change (CGI-C) by Caregiver						X		X	X
Clinical Global Impression of Change (CGI-C) by Patient[13]						X		X	X
Columbia-Suicide Severity Rating Scale	X		X	X	X	X	X	X	X
Documentation of concomitant medication[14]	X		X	X	X	X	X	X	X
Documentation of AEs	X		X	X	X	X	X	X	X
Dispensing of study drug				X	X[15]				
Intake of study drug at site				X[16]					
Return of study drug					X	X			X
Study drug compliance check					X[17]	X[18]			X[18]

[1] If the patient's eligibility is confirmed and their urine screen for N-Acetyl-D-Leucine is below the permitted threshold. The next visit, **Visit 2,** should be planned 14 days (+7) days from Visit 1.

[2] All assessments must be done pre-dose

[3] At **Visit 2,** confirm no prohibited medications since **Visit 1**

[4] If the patient (or caregiver) states the patient has been using prohibited medication at **Visit 1** or **Visit 2,** they will be classified as non-compliant and withdrawn from the study

[5] If feasible, repeat assessments performed at treating physician's discretion if clinically significant results at **Visit 3**

[6] Analyzed at PK lab

[7] Patients whose Visit 1 urine sample detects limits of N-Acetyl-D-Leucine above the permitted threshold are classified as non-compliant and withdrawn from the study

[8] Analyzed at central lab

[9] Only for post-menopausal women of non-child bearing potential with amenorrhea for at least 1 year prior to the first dose (and have not undergone sterilization procedures at least 6 months prior to the first dose)

[10] Only for women of childbearing potential; done at site

[11] In Europe only

[12] At Visit 1 through Visit 6 (*not* Visit 0) two subtests, the 9-hole Peg Test of the Dominant Hand (9HPT-D) and 8-meter Walk Test (8MWT) will be videoed in a standardized format at every visit.

[13] If the patient is able to provide the CGI-S/C

[14] Any concomitant medication needs to be recorded, used or not used for (symptoms of) A-T since the last 60 days prior screening, up to End of Study / ET

[15] If needed

[16] Patient should not have used any of the prohibited concomitant medication 42 days prior to first dose of study drug, and have had a urine screen for N-Acetyl-D-Leucine below the permitted threshold prior to first dose of study drug.

[17] If feasible

[18] Or after the Visit if IMP is returned via courier

2.5.2 Extension Phase

Period in the Extension Phase (EP)	EP Baseline Period		EP Treatment Period I			EP Wash-Out Period	EP Treatment Period II		EP Early Term.
Duration of the whole period	1 Day	1 Day	1 Year			6 Weeks	1 Year		1 Day
Visit number	Visit 7A[1]	Visit 7B	Visit 8	Visit 9A	Visit 9B	Visit 10	Visit 11	Visit 12 / EOS	ET
Name of the Visit	EP Screening/Bsl	EP Baseline	EP Treatment 1	EP Treatment 2	EP Treatment 2	EP Washout 1	EP Treatment 3	EP Treatment 4	EP ET
Timeline (Days)	*Day -1*	*Day 1, Start IMP*	*Day 180*	*Day 365*	*Day 366*	*Day 407*	*Day 587*	*Day 767*	*XX*
Visit Window allowed	*ng*	*+6 days*[2]	*+/- 14 days*	*+/- 14 days*	*ng*	*+14 days*	*+/- 14 days*	*+/- 14 days*	*ng*

Patient information and informed consent process	X					X			
Inclusion / exclusion criteria	X								
Patient Weight		X	X		X	X	X	X	X
Physical Examination		X	X		X	X	X	X	X
Documentation of concomitant medication	X		X		X	X	X	X	X
Documentation of frequency of therapy (hours per week)	X		X		X	X	X	X	X
Vital signs	X		X		X	X	X	X	X
12-lead electrocardiogram (ECG)				X					X
Blood safety laboratory tests[21]	X		X		X	X	X	X	X
Blood samples for research purposes	X				X			X	X
PK Blood Sampling[V]		X			X				
Urinalysis	X		X	X		X	X	X	X
Urine by dipstick for pregnancy test[c]	X		X	X		X	X	X	X
Urine test for N-Acetyl-D-Leucine	X					X			X
Quality of Life EQ-5D-5L for patients aged ≥18; EQ-5D-Y for children aged <18 years[11]	X		X	X		X	X	X	X
Scale for Ataxia Rating (SARA)	X		X	X		X	X	X	X

Scale for Spinocerebellar Ataxia Functional Index (SCAFI)	X		X	X		X	X	X	X
Video-Recording Primary Anchor Tests (8MWT + 9HPT-D)	X[vii]		X	X		X	X	X	X
Columbia Suicide Severity Rating Scale (CSSR-S)	X		X	X		X	X	X	X
Clinical Global Impression of Severity (CGI-S) by Physician	X		X	X		X	X	X	X
Clinical Global Impression of Severity (CGI-S) by Caregiver	X		X	X		X	X	X	X
Clinical Global Impression of Severity (CGI-S) by Patient	X		X	X		X	X	X	X
Clinical Global Impression of Change (CGI-C) by Physician			X	X		X	X	X	X
Clinical Global Impression of Change (CGI-C) by Caregiver			X	X		X	X	X	X
Clinical Global Impression of Change (CGI-C) by Patient			X	X		X	X	X	X
Documentation of AEs	X	X	X	X	X	X	X	X	X
Dispensing of study drug		X	X			X	X		
Intake of study drug at site		X			X	X			
Return of study drug[viii]			X		X		X	X	X
Study drug compliance check			X		X		X	X	X

Abbreviations: EP = Extension Phase; na = not applicable.

[i] Visit 7A may be taken from Visit 6, provided Visit 7B is scheduled within 1 day (+6 days) of Visit 6

[ii] if Visit 7B cannot be scheduled 1 day (+6 days) after Visit 6 (Visit 7A), Visit 7A and Visit 7B should be conducted over a two-day period on two consecutive days, i.e. Visit 7B occurs +1 day after Visit 7A

[iii] Analyzed at central lab

[iv] Analyzed at PK lab

[v] Only for women of childbearing potential; done at site

[vi] If a patient turns 18 over the course of the study, they should continue to use the EQ-5D-Y

[vii] If Visit 7A is based on Visit 6 assessments, the video recordings from Visit 6 should be used

[viii] Or after visit if IMP is returned via courier

[ix] If applicable

3 SUBJECTS FOR ANALYSIS

3.1 Parent Phase: Analysis populations

3.1.1 Intention-to-Treat (ITT) population

The ITT population will consist of all patients who receive at least one dose of study drug (N-Acetyl-L-Leucine) and with one video recording at either Visit 1 or Visit 2 (or both).

The ITT population will be used only for baseline summary tables.

3.1.2 Modified Intention-to-Treat (mITT) population

The mITT population will consist of all ITT patients with a video recording at either Visit 3 or Visit 4 (or both).

3.1.3 Per Protocol Set (PPS)

The PPS will consist of all patients with two video recordings at baseline (Visit 1 and/or Visit 2), end of treatment (Visit 3 and/or Visit 4), and end of washout (Visit 5 and/or Visit 6) and without any major protocol deviations that can influence the validity of the data for the primary efficacy variable.

3.1.4 Safety Analysis Set (SAF)

The Safety Analysis Set (SAF) will consist of all patients who receive at least one dose of study drug (N-Acetyl-L-Leucine).

3.2 Extension Phase: Analysis populations

3.2.1 Modified Intention-to-Treat (mITTe) population

The modified intention-to-treat analysis set Extension Phase (mITTe) will consist of all patients who receive at least one dose of study drug (N-Acetyl-L-Leucine) in the Extension Phase with a SARA score at Visit 7 of the Extension Phase and either at Visit 8 or Visit 9 (or both)

3.2.2 Safety Analysis Set (SAFe)

The Safety Analysis Set Extension Phase (SAFe) will consist of all patients who receive at least one dose of study drug (N-Acetyl-L-Leucine) in the Extension Phase

3.3 Protocol deviations

Major protocol deviators for the Parent Phase will be identified to the extent possible by individuals responsible for data collection/compliance, and its analysis and interpretation. Any patients excluded from the PPS analysis will be identified, along with their reason for exclusion.

3.4 Blind Data Review Meeting

The patients will be classified during the Blinded Data Review Meeting (BDRM) to the analysis populations using the protocol deviations. Invitees to this meeting are the Sponsor's Medical Expert, the Sponsor's representative, the Sponsor's Project Manager (PM), the Medical Monitor, the Sponsor statistician and the [redacted] statistician, but more roles can be invited if considered

necessary. Input to this meeting will be supplied by the involved Data Management provider or the responsible PM at least one week in advance of the meeting: a blinded list of all protocol deviations (including missing and likely erroneous data), with specific detailing and description regarding the deviation, preferably in Excel.

Possible compliance issues and unforeseen or reclassification of categories for missingness of the primary endpoint data will be part of the discussions held at the meeting.

Where possible, this meeting will be held in a blinded manner, that is blind to study outcome data (also for open studies). The goal of this meeting is to reach consensus on minor and major protocol deviations. In case of a major deviation impacting the primary or key secondary endpoints, the specific patient will be excluded from the PPS population. The meeting must be held prior to database lock of the Parent Phase.

The decisions taken during this meeting and the reasons for those decisions will be documented by the PM (or a delegate as agreed) and sent for review to all parties involved as soon as possible after the meeting, but before database lock. If all parties involved agree, then the document is finalized, signed and stored before database lock.

4 STUDY ENDPOINTS

4.1 Parent Phase

4.1.1 Primary endpoint

The primary efficacy endpoint is based on the blinded raters' Clinical Impression of Change in Severity (CI-CS) score on either the 9 Hole Peg Test of the Dominant Hand (9HPT-D) or the 8 Meter Walk Test (8MWT). The primary endpoint is defined as the CI-CS comparing Visit 4 with baseline (Visit 2) **minus** the CI-CS comparing Visit 6 with Visit 4.

4.1.2 Key secondary endpoints

The key secondary endpoint is the difference in the blinded rater's Clinical Impression of Severity (CI-S) values from baseline (average of Visit 1 and Visit 2) to end of treatment (average of Visit 3 and Visit 4) and from end of treatment (average of Visit 3 and Visit 4) to end of washout (average of Visit 5 and Visit 6).

4.1.3 Supportive secondary endpoints

Supportive secondary endpoints that directly supplement the analysis of the primary endpoint will be evaluated as follows:

- The individual components of the primary endpoint, that is the CI-CS from Visit 2 to Visit 4 and the CI-CS from Visit 4 to Visit 6.
- Improvement will be evaluated based on the change in the blinded raters' Clinical Impression of Severity (CI-S) between baseline (average for Visit 1 and Visit 2) and end of treatment with N-Acetyl-L-Leucine (average for Visit 3 and Visit 4) minus the change in CI-S between end of treatment with N-Acetyl-L-Leucine (average for Visit 3 and Visit 4) and end of washout (average for Visit 5 and Visit 6). Statistical testing for the primary anchor test CI-S endpoint will be as for the primary endpoint.

- Measurement of change in performance of the CI-CS score of either the 9HPT-D or the 8MWT reclassified to a 3-point scale. (As a sensitivity analysis to the primary endpoint.)
- An evaluation of the CI-CS for the test (9HPT-D or 8MWT) that was not selected as the primary anchor test.

4.1.4 Additional secondary endpoints

For all additional secondary endpoints, the change from Visit 2 to Visit 4 and the change from Visit 4 to Visit 6 will be evaluated.

Measurement of Ataxia and Functioning

- Spinocerebellar Ataxia Functional Index (SCAFI).
  The SCAFI is composed of the 8MWT, the 9HPT, and the PATA rate, a measure of speech performance.
- Scale for Assessment and Rating of Ataxia (SARA) score.
  SARA has 8 items that are related to gait, stance, sitting, speech, finger-chase test, nose-finger test, fast alternating movements and heel-shin test.

Measurement of Health-related Quality of Life

- Quality of Life EQ-5D-5L for patients aged ≥18; EQ-5D-Y for children aged 6-17 years (two parts: the EQ visual analogue scale (EQ-VAS) and the EQ descriptive system).

Measurement of Global Impression

- Clinical Global Impression of Severity by the treating physician (CGI-S-physician) at every visit.
- Clinical Global Impression of Change by the treating physician (CGI-C-physician) comparing end of treatment (Visit 4) to baseline (Visit 2), and end of washout (Visit 6) to end of treatment (Visit 4).
- Clinical Global Impression of Severity by the caregiver (CGI-S-caregiver) at every visit.
- Clinical Global Impression of Change by the caregiver (CGI-C-caregiver) comparing Visit 4 to Visit 2 and Visit 6 to Visit 4.
- Clinical Global Impression of Severity by the patient (CGI-S-patient) at every visit *if they are able.*
- Clinical Global Impression of Change by the patient (CGI-C-patient) comparing Visit 4 to Visit 2 and Visit 6 to Visit 4 *if they are able.*

The CGI-S scales are on a 7-point scale ranging from 'normal, not ill at all' to 'among the most ill patients'. The CGI-C scales are also on a 7-point scale ranging from 'very much improved' to 'very much worse'.

4.1.5 Exploratory endpoints

Sparse PK sampling will be collected for biochemical analysis so to characterize the pharmacokinetics of N-Acetyl-L-Leucine in patients with Ataxia-Telangiectasia. Analysis and reporting of pharmacokinetic is outside the scope of this analysis plan. PK data collection, data handling, analysis and reporting will be done by [redacted]. The PK report will be added to appendix 16.1 of the CSR as a separate document.

4.1.6 Safety endpoints

The safety parameters to be evaluated are:

- Adverse Events

- Laboratory safety measurements: haematology, clinical chemistry, urinalysis
- Vital signs, including orthostatic blood pressure
- ECGs
- Physical Examination
- C-SRSS

4.2 Extension Phase

With respect to the Parent Phase, all endpoints for the Extension Phase are considered secondary to the endpoints of the Parent Phase. For the most part, the same clinical outcome assessments used during the Parent Phase will be used during the Extension Phase. However, some of the existing efficacy parameters have been updated for use in the Extension Phase, as well as additional efficacy parameters that have been added.

4.2.1 Primary endpoint

The primary endpoint in this Extension Phase is success measured on the Scale for the Assessment and Rating of Ataxia (SARA) from the Extension Phase baseline (Visit 7) to the end of treatment in the Extension Phase (Visit 9).

4.2.2 Secondary endpoints

Long-term safety will be assessed via Adverse Events, Laboratory safety measurements (haematology, clinical chemistry, urinalysis), Vital signs, ECGs, Physical Examination and C-SRSS.

Full PK sampling will be conducted during the Extension Phase. Pharmacokinetics of N-Acetyl-L-Leucine in patients with A-T at Visit 7 and Visit 9 will be determined. (Note that analysis and reporting of pharmacokinetics is outside the scope of this analysis plan. PK data handling, analysis and reporting will be done by an external company that specializes in PK analysis and reporting. The PK report will be added to Appendix 16.1 of the CSR as a separate document.)

4.2.3 Exploratory endpoints

For all exploratory endpoints, the absolute values and the change from Visit 7 to Visit 9 will be evaluated.

Measurement of Neurological Symtpoms and Functioning

- Spinocerebellar Ataxia Functional Index (SCAFI).
  The SCAFI is composed of the 8MWT, the 9HPT, and the PATA rate, a measure of speech performance.

Measurement of Health-related Quality of Life

- Quality of Life EQ-5D-5L for patients aged ≥18; EQ-5D-Y for children aged 6-17 years (two parts: the EQ visual analogue scale (EQ-VAS) and the EQ descriptive system).

Measurement of Global Impression

- Clinical Global Impression of Severity by the treating physician (CGI-S-physician) at every visit.
- Clinical Global Impression of Change by the treating physician (CGI-C-physician) comparing Visit 9 to Visit 7

- Clinical Global Impression of Severity by the caregiver (CGI-S-caregiver) at every visit.
- Clinical Global Impression of Change by the caregiver (CGI-C-caregiver) comparing Visit 9 to Visit 7
- Clinical Global Impression of Severity by the patient (CGI-S-patient) at every visit *if they are able.*
- Clinical Global Impression of Change by the patient (CGI-C-patient) comparing Visit 9 to Visit 7 *if they are able.*

Further exploratory endpoints may be based on the above list, presenting changes over Visit 7 to Visit 10, Visit 9 to Visit 10, Visit 10 to Visit 12 and Visit 1 (baseline from Parent Phase) to Visit 12.

Videos of the primary and non-primary anchor tests are collected throughout the Extension Phase for the CI-CS. These videos may be analyzed in order to inform the development and validation of the CI-CS, but any further analysis will not be undertaken for the Extension Phase.

5 PARENT PHASE: STATISTICAL ANALYSIS

5.1 General considerations

The parent study is considered the study period between screening (Visit 0 or Visit 1) through Visit 6.

Raw data (in listings) will be presented in the same precision as received. Appropriate rounding will be performed for the following summary statistics, where applicable: mean, standard deviation (SD) and two-sided 95% confidence limits will be presented with at least one more decimal than the original data; minimum and maximum values will be presented with the same precision as the original data. In frequency tables, percentages will be presented with 1 decimal unless otherwise stated.

P-values will be presented with 3 decimals, and those smaller than 0.001 will be replaced by <0.001. One-sided p-values smaller than 0.05 will be considered statistically significant for the primary endpoint and indicative for other endpoints. No adjustment for multiple comparisons will be applied. Conclusions regarding treatment efficacy will not solely rely on detecting statistical significance but equal emphasis will be placed on the magnitude and clinical relevance of treatment differences as judged by the point estimates. The key secondary endpoint will be tested confirmatory if the null hypothesis concerning the primary objective is rejected. All other evaluations will be exploratory in nature.

Descriptive statistics presented in general summary tables will be the number of non-missing observations (n), mean, SD, minimum, median and maximum for quantitative data. For categorical data, frequency counts and percentages will be determined.

In general, baseline is defined as the value measured prior to first study treatment administration (at Visit 2), unless otherwise specified. In case no value at Visit 2 is available, the value measured at Visit 1 will be used. A footnote will be added to those tables/listings presenting baseline value, with an explanation how this value was assessed.

If available in the database, data for screening failures will not be presented in summary tables, except for disposition and end-of-study displays. Data for screening failures will be listed as available.

A treatment emergent adverse event (TEAE) is defined as an adverse event that appears during or after study treatment and was absent before.

5.2 Limited analyses for potential abbreviated CSR

The presented analyses in this SAP will be performed in full, unless it is decided by the Sponsor IntraBio that the study will be aborted. In this scenario, following ICH E3 and the applicable FDA guidance on abbreviated report, an abbreviated clinical study report will be created, and as a consequence the analyses to be performed may be limited as well. The analyses performed may then be restricted to:

- Presentation of the primary endpoint analysis from the Parent Study as proposed in this SAP
- Presentation of the key secondary analyses from the Parent Study as proposed in this SAP
- Presentation of the primary endpoint analysis from the Extension Phase as proposed in this SAP
- Presentation of disposition, demographics and baseline characteristics as proposed in this SAP for both the Parent Phase and the Extension Phase
- Presentation of full safety as proposed in this SAP for both the Parent Phase and the Extension Phase

Presentation may consist of descriptive statistics and listings only.

5.3 Adjudication of endpoint data

Each individual video (CI-S) or video pairing (CI-CS) will be read by two independent reviewers. The independent raters will be given 6 videos of the patient's performance of the primary anchor test taken at Visit 1 to Visit 6. The videos will be labeled as Video A, B, C, D, E, F. The videos will be presented in a random order, and the independent raters will be blinded to the timepoint corresponding to each video. The appropriate Likert scale score will be provided to each of the videos and pairs of videos.

For the CI-CS assessment, pairs of videos will be evaluated with the Likert scale defined as:

- Significantly Improved (Score = +3)
- Much Improved (Score = +2)
- Minimally Improved (Score = +1)
- No Observable Change (Score = 0)
- Minimally Worse (Score = -1)
- Much Worse (Score = -2)
- Significantly Worse (Score = -3)

For the CI-S assessment, individual videos will be evaluated with the Likert scale defined as:

- Normal, not at all ill (Score = +3)
- Borderline ill (Score = +2)
- Mildly ill (Score = +1)
- Moderately ill (Score = 0)

- Markedly ill (Score = -1)
- Severely ill (Score = -2
- Among the most extremely ill patients (Score = -3)

Each individual video (CI-S) or video pairing (CI-CS) will be read by two independent reviewers, and the appropriate Likert scale score will be entered into the eCRF.

Once each review is completed the scores will be compared. For CI-CS, if there is a difference of one (1) point in the two primary blinded reviewer scores, the two scores will be averaged. If there is difference greater than one (1) point between the two primary blinded reviewer scores for a specific video timepoint or pairing, an adjudication read will be triggered. In such cases, a third blinded reviewer will review the scores given from each of the two primary independent reviewers and determine which score is most accurate, that of reviewer A or reviewer B (adjudication by consensus). The adjudicator's decision will be the final score for that video assessment.

For the CI-S, if there is a difference between the two primary blinded reviewers scores, the two scores will be averaged.

5.4 Missing data

Patients that withdraw from the study are replaced at the discretion of the sponsor. Data from withdrawal patients will be included in the analysis until their last assessment.

For handling missing data of the statistical analyses applied to the primary and key secondary endpoints, refer to the respective analysis sections.

For endpoints being presented with descriptive statistics only, no imputation will be performed. All these analyses will be performed on data available at the visit considered. In summary tables, the number of patients without missing data will be presented (per visit, if applicable) unless otherwise specified. In calculations of percentages, subjects with missing data will not be considered in numerator or denominator unless otherwise specified.

Using the most conservative approach, missing/incomplete information related to AEs will be handled as listed below, to indicate an AE as being treatment emergent or presented having a certain intensity/causality. Note that the imputed dates or intensity/causality will not appear in data listings, but only in descriptive statistics tables (where applicable).

- In case of (partially) missing onset dates, the AE will be handled as follows:
    - If full start date is available, and on or after first dosing date, the AE is considered treatment emergent.
    - In case full stop date is available and prior to first dosing date, the AE is considered prior.
    - If the day part of the start date is missing:
        - The AE is considered treatment emergent if the month and year of the start date are the same or after the month and the year of the first dosing date.
    - If the day and month part of the start date are missing:
        - The AE is considered treatment emergent if the year of the start date is the same or after the year of the first dosing date.
    - In case the start date is completely missing:

        - If stop date is fully available and on or after the first dosing date, the AE is considered treatment emergent.
        - If the stop date is partially missing, but the month and year (or year alone in case of missing month) are after the month and year (or year alone) of the first dosing date, the AE is considered treatment emergent.
    - In case full start date and full stop date are missing, the AE is considered treatment emergent.

- In case intensity is missing for a certain TEAE, this will be regarded as severe.
- In case causality is missing for a certain TEAE, this will be regarded as related.
- In case seriousness is missing for a certain AE, this is discussed and addressed prior to database lock and unblinding in agreement with the sponsor and data management provider.

Regarding prior/concomitant medication, a similar approach will be followed for partially missing dates, as will be done for AEs as described above. If a comedication is started and stopped prior to the first date of study treatment (i.e. first dosing date), this is considered prior.

Based on the BDRM, certain values can be decided to be excluded from analyses. These values will be listed, but not included in descriptive statistics, plots or statistical analyses. This may be outlier data that are a result of unambiguous measurement errors.

5.5 Interim analysis

A formal interim analysis is not planned for this study. However, per patient data listings and possibly plots will be provided for the several DSMB meetings and as specified in the DSMB Charter.

5.6 Baseline characteristics

5.6.1 Inclusion/exclusion criteria

An individual patient listing of the deviations from inclusion and exclusion criteria will be presented.

5.6.2 Demographics

Demographic data at baseline will be summarized for all patients and by the 4 age/weight/dosing groups in tabulations.

Appropriate descriptive statistics for age, height, weight, BMI, ethnic group and sex will be given. The summary will be created for each analysis population separately. Additionally, demographic data will be listed.

5.6.3 Baseline characteristics

The following relevant patient baseline characteristics will be listed and summarized overall (frequency and percentage) and are considered key subgroups:

- Naïve versus non-naïve: trial classification/at screening
- Age (paediatric versus adult)
- Gender (male versus female)

- Age/weight/dosing group
- Disease severity based on SARA below/above the median SARA score at Visit 1
- Region (US versus EU)
- Selected Anchor Test (9HPT-D or 8MWT)
- Composite of SARA Subtests 1- 4 (Gait, Stance, Sitting, Speech): classification based on below/above the median value.
- Intra-Patient variability between SARA score at Visit 1 (Baseline 1) vs Visit 2 (Baseline 2): classification based on below/above the median value of the difference between the two visits.
- Intra-patient variability between CI-S score Visit 1 (Baseline 1) vs Visit 2 (Baseline 2): classification based on below/above the median value of the difference between the two visits.

5.6.4 Disposition

A summary table will be created, stating the number of patients per site, including site number, location/country and investigator.

To present disposition, a summary of all included, randomised, treated and completed patients will be created. Number/percentage screened will be included as well (if available in the database). Additionally, in the same summary, the number/percentage of patients in the ITT, mITT, PPS and SAF will be presented. Furthermore, the frequency and percentage per reason for non-completion will be added.

Additionally, a listing displaying all disposition information (including reasons for withdrawal and reasons for exclusion from the analysis population, if available electronically) on a per patient level will be created. This listing will include follow-up time for each patient, calculated from date of first dose until end of study.

5.6.5 Medical history

Medical history will be tabulated per System Organ Class (SOC) and Preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology list and presented as number/percentage of patients in each SOC and PT for the SAF. SOC and PT will be presented in descending order of frequency of occurrence based on SOC and PT. These data will also be listed on a per patient level.

A-T specific history will be summarized and listed as appropriate.

5.6.6 Pregnancy data

Pregnancy test result data will be listed for females of childbearing potential only, on a per visit basis.

5.6.7 Other screening data

Other data collected at screening and/or baseline only, if available, will be listed. These screening/baseline data will be presented using all subjects included in the study, if applicable.

5.7 Statistical analysis primary and key secondary endpoints

The primary analysis population is the mITT for the primary and all secondary endpoints. Analyses of these endpoints based on the PPS will also be undertaken to provide supplementary information on efficacy.

Analyses of the primary and key secondary endpoints based on the mITT population will utilise a last observation carried forward (LOCF) approach for missing/unreadable videos at Visit 5 and Visit 6. For the primary endpoint CI-CS this implies that the CI-CS value for Visit 4 to Visit 6 will be assigned the value 0 (stable) if both videos at Visit 5 and Visit 6 are unavailable.

Also, for the key secondary endpoint, CI-S based on Averaged Clinical Impression of Severity it is assumed that if both videos are missing/unreadable for the baseline (Videos from Visit 1 or 2), treatment (Videos from Visit 3 or 4), or washout (Videos from Visit 5 or 6) period, the average change from one period to another will be assigned the value 0 (stable).

A sensitivity analysis for missing data will be performed to compare patient's outcome on the primary outcome and key secondary measures and their compliance throughout the study. The robustness of the primary analyses of the primary and key secondary endpoint in the mITT analysis set will be assessed as follows:

- If either video for Visit 3 or Visit 4 is available but both videos for Visit 5 and Visit 6 are not available, then the value -1 (worsening) will be used instead of 0 for the CI-CS for Visit 4 to Visit 6 unless the missingness is due to a technical reason (MCAR, e.g. due to machine failure).

For each of the primary and secondary endpoints there will be separate descriptive statistical displays within the key subgroups as listed in section 10.1, without any statistical analysis. For the subgroup presentations, only the mITT population will be used. Spaghetti plots will not be created for the subgroup analyses; these will be presented in forest plots (one for each endpoint, excluding the SARA - and SAFI subscores and excluding the EQ-5D-5L/Y), presenting the mean or (pseudo-)median with a 95% CI, using a stem at mean or median difference of 0, where applicable. Upon discretion of the programmer, the forest plots may be presented as two plots: one for Visit 4 versus Visit 2 and one for Visit 6 versus Visit 4.

Considering the number of subgroups, the forest plots may become unclear and indecipherable. When that occurs, a split will be made into two forest plots for the endpoints: one for the first 7 subgroups, and one for the remaining.

All individual primary and secondary endpoint data will be listed as well.

5.7.1 Primary endpoint

The primary efficacy endpoint is based on the blinded raters' Clinical Impression of Change in Severity (CI-CS) score over 6 weeks determined by comparing videos showing the patient's performance on a pre-defined anchor clinical symptom scale: either the 9 Hole Peg Test of the Dominant Hand (9HPT-D) or the 8 Meter Walk Test (8MWT).

For each patient, there will be two CI-CS scores. These two scores indicate the level of change in severity observed in Visit 4 (end of treatment) compared to Visit 2 (baseline) and the level of

change in severity observed in Visit 6 (end of washout) compared to Visit 4 (end of treatment). Both CI-CS scores are measured on a 7-point Likert-point scale (-3 = *significantly worse* to +3 = *significantly improved*, see section 5.3 for the precise definition) and the primary endpoint is defined as the difference between both CI-CS scores.

The primary endpoint will be summarized using descriptive statistics, including a frequency table, and frequency percentages will be presented graphically using a bar chart.
The primary statistical analysis will be performed using a one-sample t-test comparing the CI-CS difference score to zero. Statistical output will present the number of patients included in the analysis, both CI-CS scores, the mean of the difference, the corresponding 95% confidence interval, and a one-sided p-value.

The assumption of normality will be visually checked and if the assumption does not hold, a Wilcoxon signed-rank test will be performed instead of the t-test using the difference score. Statistical output will then present the number of patients included in the analysis, both CI-CS scores, the (pseudo-)median of the difference using the Hodges-Lehmann estimator, the corresponding 95% confidence interval, and a one-sided p-value.

5.7.2 Key secondary endpoint

The key secondary endpoint will be presented using the mITT,and PPS populations.

Change in severity score based on Averaged Clinical Impression of Severity (CI-S)
CI-S scores are measured on a 7-point Likert-point scale (-3 = *among the most extremely ill patients* to +3 = *normal, not at all ill*; see section 5.3 for the precise definition).

Improvement in the pre-defined anchor test measure will be evaluated based on the change in the blinded raters' CI-S scores between baseline (average for Visit 1 and Visit 2) and end of treatment (average for Visit 3 and Visit 4) minus the change in CI-S between end of treatment with N-Acetyl-L-Leucine (average for Visit 3 and Visit 4) and end of washout (average for Visit 5 and Visit 6). The presentations and statistical analyses will be similar to the primary endpoint, including the sensitivity analysis.

5.7.3 Supportive secondary endpoints

The supportive secondary endpoints will be presented using the mITT,and PPS populations, according to randomized treatment.

Clinical Impression of Change in Severity
The CI-CS scores on the pre-defined anchor test for Visit 4 versus Visit 2, and the CI-CS score on the pre-defined anchor test for Visit 6 versus Visit 4 will be analysed separately. These secondary endpoints will be summarized using descriptive statistics and frequency tables, and percentages will be shown graphically using a bar chart. No sensitivity analysis will be applied.

Clinical Impression of Change in Severity reclassified on a 3-point scale
Using the CI-CS outcome on the pre-defined anchor test based on the data for Visits 2 and Visit 4, any patient given a score of -1, -2, or -3 on the CI-CS will be classified as worsened (< 0). Any patient classified as 0 on the CI-CS will be classified no change (0). Any patient given a

score of +1, +2, +3 on the CI-CS will be classified as improved (> 0). Similarly, the CI-CS comparing Visit 4 and Visit 6 will be reclassified and the differences between these two scores on a 3-point scale will be calculated.
The descriptive table and graphical presentations will be similar to the primary endpoint. No statistical analysis will be performed, and no sensitivity analysis will be applied.

Clinical Impression of Change in Severity (CI-CS) score non-primary anchor test
Descriptive statistics and frequency tables of the CI-CS scores for the test (9HPT-D or 8MWT) that was not selected as the primary anchor test will be presented for Visit 4 versus Visit 2, and separately, for Visit 6 versus Visit 4. No plots will be created, and no sensitivity analysis will be applied.

5.7.4 Additional secondary endpoints

All additional secondary endpoints will be presented using the mITT and PPS populations, and all individual data will be listed as well. No sensitivity analysis will be applied.

Measurement of Ataxia and Functioning

- SARA total score
- SCAFI total score
  - 9HPT-D
  - 9HPT-ND
  - 8MWT
  - PATA test

Descriptive statistics will be used to summarize the endpoints above at each visit.

The subscores of the SARA score (gait, stance, sitting, speech disturbance, finger chase, nose-finger test, fast alternating hand movements, heel-shin slide) will also be summarized for each visit using descriptive statistics. Stacked bar charts will be provided per visit, based on the subscores of the total SARA score.

Spaghetti plots of individual patient SARA total scores and the SCAFI total scores versus time will be made as well as a mean or median display versus time, depending upon the distribution, and corresponding 95% CI at each visit.

The average SCAFI subscores (8MW_avg, 9HPT-D_avg, 9HPT-ND_avg and PATA_avg) as determined according to section 10.1, following the scoring manual, will also be summarized with descriptive statistics.

The changes in SARA total score, SCAFI total score, the SCAFI subscores (8MW_avg, 9HPT-D_avg, and PATA_avg) between Visit 2 and Visit 4, as well as the changes between Visit 4 and Visit 6 will be analysed using a one-sample t-test or a Wilcoxon Signed Rank test depending on the distribution of the data. The SCAFI subscore 9HPT-ND_avg will only be descriptively summarized in tabular format.

Measurement of Health-related Quality of Life
The results of EQ-5D-5L as well as the EQ-5D-Y will be combined into a 5-digit number presenting the health status of the subject. Frequency tables will be presented per visit for the 5 domains, as well as for the 5-digit number of the EQ-5D-5L and the EQ-5D-Y separately.

In addition, EQ-5D-5L and EQ-5D-Y domain percentages will be presented in separate bar charts per visit, with all visits combined into one plot (if possible).

The EQ-VAS score will be summarized by visit using descriptive statistics for patients aged < and ≥18 years, consistent with the EQ-5D questionnaires. Spaghetti plots of individual patient EQ-VAS scores versus time will be made as well as a mean or median display versus time, depending upon the distribution, and corresponding 95% CI at each visit.

Measurement of Global Impression

The three CGI-S scores (scored by treating physician, caregiver and patient) will be summarized using descriptive statistics and frequency tables for each visit.
Bar charts will be presented for the three CGI-S scores, spaghetti plots of individual CGI-S scores versus time will be made as well as a mean or median display versus time, depending upon the distribution, and corresponding 95% CI at each visit.

Descriptive statistics and frequency tables will also be used to summarize the three CGI-C scores (treating physician, caregiver and patient) between Visit 2 and Visit 4, and between Visit 4 and Visit 6, and corresponding bar charts will be created.

Changes in CGI-C score will further be statistically analysed with a one-sample t-test or a Wilcoxon Signed Rank test. Note that CGI-C is mentioned as CGI-I in the CRF.

It is important to realize that the CGI-S and CGI-C scores per visit for each patient as provided by the caregiver may be based on varying caregivers and hence additional variation is introduced. No correction for this variation can be done using the above statistical methods. A footnote will be added to the table to describe this situation.

5.7.5 Other additional statistical analyses

The following analyses will provide an estimate of intra-patient variability and provides information on the stability of the outcome evaluation. Note that, considering the high degree of variability within and between these patients, this is only a simple approach as results may be influenced by e.g. rater variability, disease progression or treatment effect.

The analysis will be done for the mITT population only, and only for the CI-S outcome of the videos. No sensitivity analysis will be applied, and no separate analysis will be performed for subgroups.

The Intraclass Correlation Coefficient (ICC) will be used as an index of reliability to measure agreement between pairs of observations for Visit 1 and 2, Visit 3 and 4, and Visit 5 and 6 respectively, presenting the proportion of the total variance in the observations that is due to the differences between pairs. The ICC takes on values between 0 (meaning no agreement) to 1 (perfect agreement), with and ICC >0.80 representing high reliability. No imputation for missing visits will be done, and the ICC can only be determined for subjects having data for both visits in the pairs. The ICC value and the corresponding 95% confidence interval will be presented in a tabular format, and for additional clarity the number of available pairs will be added as well.

5.8 Safety and tolerability evaluation

All safety analyses will be presented using the SAF, according to actual treatment received.

5.8.1 Adverse events

A treatment emergent adverse event (TEAE) is defined as an adverse event that appears during or after study treatment and was absent before, or an adverse event that was already present but worsens during or after study treatment relative to the pre-treatment state.

An AE overview table will be created displaying the number and percentage of subjects experiencing a treatment-emergent adverse event (TEAE) and the number of TEAEs for: any TEAE, any mild/moderate/severe TEAE, any related/unrelated TEAE, any serious AE, and any TEAE leading to study discontinuation.

Furthermore, all TEAEs will be tabulated by System Organ Class (SOC) and Preferred Terms (PTs) within each SOC according to the MedDRA terminology list, using frequency counts (number of subjects with at least one event, and number of events) and percentage of subjects with the event.

TEAEs will also be tabulated by severity (mild/moderate/severe) and by relationship to study medication (related/unrelated). Similar tables will be created for TEAEs leading to premature discontinuation, SAEs and deaths, if applicable. These summary tables will be presented by decreasing frequency of occurrence based on SOC and PT.

In addition, similar TEAE tables (overall, by severity and by relationship, premature discontinuation, SAEs, and deaths) by SOC and PT will be presented per treatment cycle, and frequencies and percentages will be determined for the active treatment cycle and the washout cycle. The treatment cycle is the period between start of first treatment at Visit 2 and 24 hours after last dose at Visit 4. The washout cycle starts 24 hours after last dose at Visit 4 until and including Visit 6.

The summary tables will be accompanied by individual subject listings of *all* AEs including information on AE number, actual AE description, date/time of start and end of AE (or ongoing), PT (MedDRA), SOC (MedDRA), severity, relationship, pre-dose (yes/no), seriousness, action taken, outcome and other information collected in the CRF for adverse events. Pre-dose AEs are not considered to be treatment-emergent, except in case of worsening during/after study treatment (to be collected as separate AE in the database). AEs starting prior to administration of the study drug will only be listed. In this listing, a clear distinction will be made between prior and treatment emergent events.

Separate listings will be created for SAEs and deaths, if applicable. The SAF population is used for the AE presentations.

5.8.2 Clinical laboratory

The following laboratory safety data are collected for this study:

Haematology	Chemistry	Urinalysis
Hemoglobin	Sodium	Leukocytes
Erythrocytes	Lactate dehydrogenase (LDH)	Nitrite
Hematocrit	Potassium	Urobilinogen
Thrombocytes	Creatinine	Protein
Leukocytes	Serum bilirubin level	pH
	AST	Occult blood (erythrocytes, leucocytes)
	ALT	Specific gravity
	Urea	Ketones

	ALP	Bilirubin
	Bicarbonate	Glucose
	Chloride	
	Calcium	
	Phosphorus	
	FSH (for postmenopausal women only)	

Laboratory safety data for haematology, biochemistry and urinalysis will be summarized using descriptive statistics and listed per visit, using protocol visits. Change from baseline will be calculated and presented as well for quantitative data, using the same summary statistics. If applicable, laboratory safety data collected as additional/unscheduled assessments (i.e. apart from those per protocol) will only be listed and will not be used in summary statistics. Baseline is defined as the Visit 2 measurement. In case the Visit 2 measurement is missing, the Visit 1 measurement will be used.

For laboratory safety data, all recorded and determined laboratory safety data will be listed, including information on the reference ranges, if available. In addition, information regarding age at screening and sex will be added to the listing.

All safety laboratory parameters will be presented in the tables and listings in the same standard units as supplied, which will be SI units.

Lastly, for clinical laboratory parameters, a listing will be created presenting all data that are out of reference range on a per-patient level, including any available unscheduled measurements. The investigator has judged the out-of-range values on their clinical significance, and this information will be added as well. Information regarding age at screening and sex will be added to this listing. The SAF population is used for the presentations.

5.8.3 Vital Signs

Vital sign data consist of measurements for pulse rate and systolic/diastolic blood pressure in sitting position. In addition, orthostatic vital sign measurements are collected (i.e. in supine and standing position). Vital signs will be summarized and listed per position and visit (protocol visits). Change from baseline will be calculated and presented as well, using the same summary statistics. Visit 2 is considered the baseline visit for vital signs; in case Visit 2 is missing, the Visit 1 measurement will be used as baseline instead. In addition, a frequency table will be created presenting patients with/without orthostatic hypotension (see definition in section 10.1) at each visit.

If applicable, vital sign measurements collected as additional/unscheduled assessments (i.e. apart from those per protocol) will only be listed and will not be used in summary statistics.

The SAF population is used for the presentations.

5.8.4 ECG

ECG outcome results (corrected QT interval and normal/abnormal result) will be presented descriptively per protocol visit. If applicable, ECG measurements collected as additional/unscheduled assessments (i.e. apart from those per protocol) will only be listed and will not be used in summary statistics. The SAF population is used for the presentations.

5.8.5 C-SSRS

The C-SSRS data are presented in two summaries. The SAF population is used for both presentations.

The first summary contains the frequency and percentage of the 5 Suicidal Ideation subscores, the Suicidal Ideation composite score, the 5 Suicidal Behavior subscores, the Suicidal Behavior composite score, the Suicidal Ideation and Behavior composite score, and the 11th question (Self-injurious behavior without suicidal intent) for each visit. Furthermore, it presents the Suicidal Ideation Score using appropriate descriptive statistics.

The second summary presents the treatment-emergent suicidal ideation and behavior compared to baseline for each visit, again presenting frequencies and percentages. Visit 2 is considered the baseline visit for C-SSRS; in case Visit 2 is missing, the Visit 1 measurement will be used as baseline instead. The *improvement in suicidal ideation* is defined as a decrease in Suicidal Ideation Score compared to baseline.
The *emergence of suicidal behavior* is defined as the occurrence of suicidal behavior (a yes on any of the questions 6-10), when there is no suicidal behavior present at baseline (all 'no' answers to any of the questions 6-10).

5.8.6 Prior and concomitant medication/therapies

The use of prior and concomitant medication/therapies will be listed for all subjects: included will be the preferred term, World Health Organization (WHO) coding information and the Anatomic Therapeutic Chemical (ATC) class code), dose, route of administration, start and stop date, frequency and reason for administration, as well as information if given for an AE. Differentiation will be made between prior and concomitant medication/therapies, by creating two separate listings. A frequency table per ATC class code and WHO drug code will be created if considered relevant, separately for prior and concomitant medication/therapies. The SAF population is used for the presentation.

5.8.7 Physical examination

General physical examination data will be listed.

5.9 Scheduled visits, dosing and treatment Compliance

5.9.1 Visit dates

A listing with actual visit dates (and times, if applicable) per patient will be presented.

5.9.2 Dosing and treatment compliance

Relevant dosing information (first dosing date, last dosing date), scheduled and actual dosing dates/times and treatment compliance information will be determined and listed for each patient. Summary statistics for the number of N-Acetyl-L-Leucine doses taken, based on bottles and/or sachets of dispensed and returned unused bottle and/or sachet counts, will be calculated for Visit 3 and Visit 4 if this information is collected on a per-visit basis. Compliance is defined as 100% * (total number of IB1001 bottles and/or sachets dispensed – total number of IB1001 unused bottles and/or sachets returned), divided by the number of bottles and/or sachets which should have been used. Note that the number of bottles and/or sachets the patients should have used depends on the dosage they should take (see section 2.3 for reference) and the duration of the treatment period. Considering the fact that the patient's total daily dose may be reduced by up to

half of their assigned dose at the discretion of the investigator, the actual dose will be used to determine the correct compliance calculation, if collected in the eCRF. The proportion of patients who take at least 80% of the prescribed medication will also be shown. Total dosing period is defined as the duration (in days) between first dose date and last dose date.

6 EXTENSION PHASE: STATISTICAL ANALYSIS

6.1 General considerations

The Extension Phase is considered the study period starting with the Extension Phase baseline (Visit 7) until Visit 12. In principle, data presentations will be created for the full Extension phase. Only where applicable and relevant, a separation will be made as follows:

- Extension phase I: Extension phase Visit 7 until Visit 10
- Extension phase II: Extension phase Visit 10 until Visit 12.

All evaluations will be exploratory in nature, and all endpoints for the Extension Phase are considered secondary to the endpoints of the Parent Phase. Statistical analysis will only be applied for some of the endpoints as defined for the Extension Phase I, and no statistical analyses will be done for the endpoints in Extension Phase II.

Summary presentations and listings will be presented and only reported data will be presented for data collected during Extension Phase. If not otherwise defined, data will be presented as missing where applicable.

Raw data (in listings) will be presented in the same precision as received. Appropriate rounding will be performed for the following summary statistics, where applicable: mean, standard deviation (SD) and two-sided 90% confidence limits will be presented with at least one more decimal than the original data; minimum and maximum values will be presented with the same precision as the original data. In frequency tables, percentages will be presented with 1 decimal unless otherwise stated.

P-values will be presented with 3 decimals, and those smaller than 0.001 will be replaced by <0.001. One-sided p-values smaller than 0.05 will be considered statistically significant for the primary endpoint and indicative for other endpoints. No adjustment for multiple comparisons will be applied. Conclusions regarding treatment efficacy will not solely rely on detecting statistical significance but equal emphasis will be placed on the magnitude and clinical relevance of treatment differences as judged by the point estimates.

Descriptive statistics presented in general summary tables will be the number of non-missing observations (n), mean, SD, minimum, median and maximum for quantitative data. For categorical data, frequency counts and percentages will be determined.

For the full Extension Phase, the measurement at Visit 7 is considered the baseline. In case of missing Visit 7A data for safety measurements (e.g. for safety lab), and Visit 7B has occurred within 1 (+6) days of Visit 6, the Visit 6 data from the Parent Study should be used instead (data are not being re-entered in the database): see also Section 2.2.2 for clarification.

No screen failures will be present in the data.

For the Extension Phase, a treatment emergent adverse event (TEAE) is defined as an adverse event that appears during or after the start of study treatment in the Extension Phase at Visit 7B

and was absent before. As a consequence, adverse events occurring during the washout phase between Visit 9 and Visit 10 will also be considered treatment emergent for the Extension Phase.

6.2 Adjudication of endpoint data

Videos of the primary and non-primary anchor tests are collected throughout the extension phase for the CI-CS. These videos may be analyzed in order to inform the development and validation of the CI-CS but will not be reported in the CSR (and hence not listed or tabulated). Data received will be included as-is in the CDISC files. In case of analysis, the following process applies: For the CI-CS assessments of both the primary and non-primary anchor tests, after a patient completes Visit 10 of the Extension phase, the independent raters will be given 3 video pairs of from Visit 7 to Visit 9, Visit 9 to Visit 10, and Visit 7 to Visit 10. After a patient completes Visit 12 of the Extension phase, the independent raters will be given a video pair from Visit 10 to Visit 12 (the raters may also assess additional video pairs, i.e. Visit 1 to Visit 12, on an exploratory basis). The videos will be presented in a random order, and the independent raters will be blinded to the timepoint corresponding to each video. The appropriate Likert scale score will be provided to each of the videos and pairs of videos. For further details regarding scoring and adjudication, which will be similar to that of the Parent study, see Section 5.3.

6.3 Missing data

Data from withdrawal patients will be included in the analysis until their last assessment.

Analyses based on the mITTe analysis set will utilize a last observation carried forward (LOCF) approach for a missing SARA score at Visit 9: Visit 8 will be use instead. For all other endpoints there will be no imputation for missing data and data will be reported and evaluated as observed. No sensitivity analysis will be applied.

Similar approaches as described in Section 5.4 will be followed for the safety analyses, with the alteration that “first dose date” is the first dosing of the Extension Phase. For AE and concomitant medication this indicates that events started during the Parent Phase and continuing during the Extension Phase will be considered prior for the Extension Phase.

6.4 Interim analysis

Except from regular deliveries to DSMB meetings, no formal interim analysis is performed on the Extension Phase data.

6.5 Baseline characteristics

6.5.1 Inclusion/exclusion criteria

An individual patient listing of the deviations from inclusion criteria will be presented. No exclusion criteria are collected for the Extension Phase, and no separate inclusion is done for Extension phase II.

6.5.2 Demographics

Demographic data at baseline Visit 7 will be summarized for all patients and by the several age/weight/dosing groups in tabulations, even if there is a change in dose between Visit 8 and Visit 12 (see Section 2.3.2).

Appropriate descriptive statistics for age, height, weight, BMI, ethnic group and sex will be given. The summary will be created for each analysis population separately. Additionally, demographic data will be listed.

6.5.3 Baseline characteristics

The following relevant patient baseline characteristics will be listed and summarized overall (frequency and percentage) and are considered key subgroups for the primary endpoint:

- Naïve versus non-naïve as determined at screening during the Parent Phase
- Age (pediatric versus adult) at Visit 7
- Age/weight/dosing group as applicable at Visit 7
- Disease severity based on SARA below/ above the median SARA score at Visit 7
- Gender (male versus female)
- Region (US versus Europe)
- Selected Primary Anchor Test (9HPT-D or 8MWT) as defined during the Parent Phase
- Individual components of SARA scale: Gait Subtest (Visit 7)
- Composite of SARA Subtests 1-4 (Gait, Stance, Sitting, Speech) : classification based on below (≤)/above the median value at Visit 7

6.5.4 Disposition

A summary table will be created, stating the number of patients per site, including site number, location/country, and investigator.

To present disposition, a summary of all included, treated, and completed patients will be created for the Extension phase I and II separately, and for the full Extension phase. Additionally, in the same summary, the number/percentage of patients in the SAFe and mITTe will be presented. Furthermore, the frequency and percentage per reason for non-completion will be added.

A listing displaying all disposition information (including reasons for withdrawal and reasons for exclusion from the analysis population, if available electronically) on a per patient level will be created. This listing will include follow-up time for each patient, calculated from date of first dose during the Extension Phase until end of Extension phase or withdrawal date.

6.5.5 Medical history

Note that only for patients not having a seamless transition from the Parent Phase to the Extension Phase, additional medical history data may be collected during the intermediate time. If applicable: medical history as collected between the Parent phase and Extension phase will be tabulated per System Organ Class (SOC) and Preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology list and presented as number/percentage of patients in each SOC and PT for the SAFe. SOC and PT will be presented in descending order of frequency of occurrence based on SOC and PT. These data will also be listed on a per patient level.

6.5.6 Pregnancy data

Pregnancy test result data will be listed for females of childbearing potential only, on a per visit basis.

6.5.7 Other screening/baseline data

Other data collected at screening and/or baseline only, if available, will be listed. These screening/baseline data will be presented using all subjects included in the Extension Phase, if applicable.

6.6 Statistical analysis efficacy endpoints

The analysis population is the mITTe for the primary and all secondary endpoints.

There will be no imputation for missing data and data will be reported and evaluated as observed.

All individual primary and secondary endpoint data will be listed as well.

6.6.1 Primary endpoint

The primary endpoint is based on the SARA score, with success defined as no change or a decrease in the SARA total score from Visit 7 to Visit 9.

It is postulated that under standard of care, 90% of patients would worsen (higher score) in terms of their performance on the SARA scale over a 12-month period, while conversely only 10% would show similar performance or some improvement. Descriptive statistics will be provided and statistical evaluation of the primary binary endpoint (success/failure on SARA scale) will compare the proportion of success with 10% in a one-sided Fishers Exact test at the one-sided 5% significance level.

In addition, the primary endpoint of success will be presented per key subgroup (see section 6.5.3), using descriptive statistics in a tabular format. For this subgroup presentation the mITTe population will be used.

6.6.2 Secondary endpoints

PK data handling, analysis and reporting will be done by an external company that specializes in PK analysis and reporting. However, listings will be created per this SAP for (sparse) PK concentration data and the urine test for N-Acetyl-D-Leucine. The PK report from the external company will be added to Appendix 16.1 of the CSR as a separate document.

Safety is described in sections 6.7, and the SAFe will be used for those presentations.

6.6.3 Exploratory Endpoints

All exploratory endpoints for the Extension Phase will be presented using descriptive statistics, per visit and comparing values at Visit 7 and Visit 9 by change from baseline derivations. Descriptive presentations will also be provided for Visit 7 to Visit 10, Visit 9 to Visit 10, Visit 10 to Visit 12 and Visit 1 (baseline from Parent Phase) to Visit 12. For any of these endpoints, no statistical analysis other than descriptive statistics will be done and no plots will be created. Where applicable, total scores, average scores and subscores will be presented.

Measurement of Ataxia and Functioning

- SCAFI total score
  - 9HPT-D
  - 9HPT-ND

- 8MWT
- PATA test

Descriptive statistics will be used to summarize the endpoints above at each visit.

The total and the subscores of the SARA score (gait, stance, sitting, speech disturbance, finger chase, nose-finger test, fast alternating hand movements, heel-shin slide) will also be summarized for each visit using descriptive statistics, including change from baseline.

The average SCAFI subscores (8MW_avg, 9HPT-D_avg, 9HPT-ND_avg and PATA_avg) as determined according to Section 10.1, following the scoring manual, will also be summarized with descriptive statistics per visit.

The changes in SARA total score, SCAFI total score, and the SCAFI subscores (8MW_avg, 9HPT-D_avg, 9HPT-ND_avg and PATA_avg) between visits will be descriptively summarized in tabular format as well.

Measurement of Health-related Quality of Life
The results of EQ-5D-5L as well as the EQ-5D-Y will be combined into a 5-digit number presenting the health status of the subject. Frequency tables will be presented per visit for the 5 domains, as well as for the 5-digit number of the EQ-5D-5L and the EQ-5D-Y separately.

Note that if a patient turns 18 before Visit 7, this patient can have results on EQ-5D-Y in the Parent Study, and results on EQ-5D-5L in the Extension phase Visit 7 to 10. For this reason, separate QoL presentations will be created for Extension phase I, using Visit 7 measurements as baselines. The EQ-VAS score will be summarized by visit using descriptive statistics in a combined manner for patients aged < and ≥18 years (using Visit 7 age values).

Measurement of Global Impression
The three CGI-S scores (scored by treating physician, caregiver, and patient) will be summarized using descriptive statistics and frequency tables for each visit.

Descriptive statistics and frequency tables will also be used to summarize the three CGI-C scores (treating physician, caregiver, and patient) between Visit 7 and Visit 9.

It is important to realize that the CGI-S and CGI-C scores per visit for each patient as provided by the caregiver may be based on varying caregivers and hence additional variation is introduced. No correction for this variation can be done and a footnote will be added to the table to describe this situation.

6.7 Safety and tolerability evaluation

The safety and tolerability evaluation for the Extension Phase is similar to what is described for the Parent Phase (see Section 5.8), with the remark that the evaluation is limited to the Extension Phase only and Visit 7 is considered the baseline. Safety and tolerability evaluations will be based on the SAFe Analysis Set.

For the AE presentation per treatment cycle, the cycles for Extension Phase are as follows:

- Treatment cycle Extension Phase Treatment Period I: the period between start of first treatment at Visit 7 and 24 hours after last dose at Visit 9.

- Washout cycle Extension Phase: starts 24 hours after last dose at Visit 9 until and includes Visit 10.
- Treatment cycle - Extension Phase Treatment Period II: the period between start of treatment at Visit 10 and 24 hours after last dose at Visit 12.
-

Note that for those patients that do not transition seamlessly to the Extension Phase, additional prior medication/adverse events may be collected at the start of the Extension Phase, and these will be presented separately from the prior medication/adverse events of the Parent Phase.

Physical examination, which is collected twice during the Extension Phase, will be presented as follows: general physical examination data will be tabulated and listed per visit. The summary table will include number/percentage of patients with normal or abnormal observations and NCS/CS frequencies/percentages for abnormal observations per visit.

C-SSRS for the Extension Phase will be presented in a similar fashion as for the Parent Phase (see Section 5.8.5).

6.8 Scheduled visits, dosing, and treatment compliance

The presentation for the Extension Phase is similar to what is described for the Parent Phase (see Section 5.9), with the remark that the evaluation is limited to the Extension Phase only and Visit 7 is considered the baseline (unless it is specifically mentioned that Visit 2 is the baseline). Compliance calculations are done for the Extension Phase with Visit 7 as reference/first dose date.

7 CHANGES TO PROTOCOL

Instead of Bland-Altman analyses of outcome scores at Visit 1 vs Visit 2, Visit 3 vs Visit 4, and Visit 5 vs Visit 6 as described in the protocol for the Parent study, an ICC method for agreement between the visits will be used instead to assess the stability of the outcome, as described in section 5.7.4. This is because no per-rater information is available in the dataset to be received, only an averaged or agreed value.

For the Parent Phase, sparse PK sampling will be collected for biochemical analysis to characterize the pharmacokinetics of N-Acetyl-L-Leucine in patients with NPC. For the extension study, full PK profiles will be collected at Visit 7 and Visit 9. Creation of descriptive displays and reporting of these data is outside the scope of this statistical analysis plan. PK concentration data and PK parameters will be included in CDISC domains, after receipt. For the Parent phase a listing of PK concentration data will be created for inclusion in the Parent phase interim CSR, since the full PK report will only be available after the end of the Extension phase. Furthermore, urine tests for N-Acetyl-D-Leucine are handled by the same lab but will be included in the clinical database and will therefore be part of the CDISC datasets.

The protocol accidentally states that “success of SARA is measured as a change in mDRS”. This is a typographical error, as mDRS is not collected for this study. This has been adjusted in this SAP accordingly.

As a supportive secondary endpoint, the protocol states *Improvement in the primary and non-primary anchor test measures will be evaluated based on the change in the blinded raters' Clinical Impression of Severity (CI-S)…* ”. However, this is incorrect as analyses on non-primary anchor are only performed for CI-CS and not the CI-S. Hence, the description of this endpoint in

the SAP is changed by removing the anchor test references and by adding the CI-CS comparison for the non-primary anchor test as endpoint, pending potential further updates of the protocol.

The investigation of the intra-rater correlation cannot be performed, since the [redacted] data do not differentiate the data per rater but rather provide an average or agreed value. Therefore, this analysis has been removed from the SAP.

Considering the primary endpoint of the Extension phase is a different one then the primary endpoint of the Parent Study, the trial is called successful only when the primary endpoint of the Parent Study is positive. All analyses of the Extension phase on data collected until Visit 10 are considered secondary to ones of the Parent Study. All presentations in the Extension phase on data collected after Visit 10 are exploratory and descriptive.

Baseline characteristics/subgroups are defined slightly different in this SAP as compared to the protocol, but only to provide more clarity on the precise subgroups and timepoints as applicable. For some patients, repeat visits were scheduled if measurements could not be fully handled during the agreed visit. Repeat visits will be listed for BDRM, and during BDRM or Clean File meeting it will be decided how the repeat data will be handled for analysis. Decisions will be documented prior to Database lock. Unscheduled visits, even if collected during the COVID pandemic, will not be used for analyses and only presented in listings.

8 COVID-19 DETAILS

This study (at least the Parent Phase) is conducted during the COVID-19 outbreak. The following data capture decisions have been taken due to national, local, or site-specific restrictions imposed due to COVID-19, with the primary need to prioritize the safety of clinical study teams and patients, and to maintain the integrity of the study/data collection.

- All protocol deviations relating to COVID-19 are collected.
- If Visit 2 is performed 8 weeks (56 days) or more after Visit 1, some Visit 1 assessments must be repeated.
- Visits 3 and 5 can be converted to remote visits (i.e. phone, video conference).
- Visits 4 and 6 can be postponed until the in-person visit is feasible and should be performed in person. Where applicable, remote data collection should be collected on the date of the original visit, as unscheduled. The postponed Visits 4 and 6 will collect all data per protocol.

Currently, the impact of COVID-19 on the proposed statistical analyses is unknown. The statistical analysis already allows some flexibility for handling missing data, however, if needed then specific items/changes related to COVID-19 will be detailed in a separate document (Addendum 1), which then will be maintained as a living document throughout the study continuation of the Parent phase and adjusted based on the duration and extent of the impact of the COVID-19 situation.

All protocol deviations related to COVID-19 will be well-documented to enable appropriate evaluation of the IB1001-203 clinical trial.

Note that no COVID-19 specific measures are taken for the Extension Phase.

9 DATA RECEIPT

All clinical eCRF data received from the Data Management provider per transfer agreement will be mapped to SDTM files. The information regarding minor/major violations will be received as excel file (a so-called "protocol deviations log") and will be transferred to SDTM as well. The blinded results on the video-recordings (blinded rater's CI-CS and CI-S) will be received from [redacted] as provider following the transfer agreement and will be mapped to SDTM. The received data will include relevant categorizations on missing data.

The SDTM files will be recoded to ADaM format, where necessary. Listings will be programmed on the SDTM and ADaM datasets as applicable, tables and figures will be programmed on ADaM datasets.

10 TECHNICAL DETAILS

10.1 Programming conventions

Programming conventions apply to both the Parent Phase as well as the Extension Phase, unless otherwise specified. Any other programming conventions that are not foreseen in preparation of this SAP, will be handled when encountered and documented separately.

General

BMI will be calculated in SAS as follows: weight/height^2, with weight in kg and height in meter (unit kg/m^2). Durations will be programmed as stated in the respective analysis sections. Where applicable, weight and height measurements will be converted to units cm and kg, using the following conversion factors: from inch to cm: multiply by 2.54, from lb to kg: multiply by 0.45359237. Variables with values representing a missing observation (such as -99, 99, 888 or 999) will be recoded to missing in SAS.

Durations, determination of baseline values and handling of missing data will be programmed as stated in the respective analysis sections.

Orthostatic hypotension is defined as a decrease of ≥20 mmHg in SBP or a decrease of ≥10 mmHg in DBP between supine and standing.

SCAFI

For 8MWT, assistance of another person or using the wall as support is not allowed. However, timed 8MWT trials for participants who used "unallowable support" (another person or the wall) are entered in the database, considering these measurements are also necessary due to their relation to the primary and a number of secondary endpoints of the study based on videos of the test. Therefore, for the SCAFI analysis, the data for these patients that used either the wall or person support during the 8MWT should be made missing.

Furthermore, patients for 9HPT, the following clinical rules apply:

- if proband cannot complete trial in 5 minutes (i.e. 300 seconds) with dominant hand, move on to the trials with non-dominant hand
- if proband cannot complete one trial in 5 minutes (i.e. 300 seconds) with non-dominant hand, discontinue 9HPT

As a consequence, if in the database values >300 are entered for Trial 1 and/or 2, the approach for handling these data in regards to SCAFI will be:

- In the case Trial 1 has a value <300 and Trial 2 has a value of >300 seconds, only the trial 1 with value <300 will be used for further analysis.
- In the case Trial 1 has a value of >300 seconds and Trial 2 has a value of <300 seconds, the data will count as missing and unable to perform due to physical limitations (as per the discontinuation rules defined above, Trial 2 should not have been conducted)
- In other instances, where only one trial is performed with a value >300 seconds, or two trials are performed with both values >300 seconds, the data will be considered missing due to physical limitations and replaced with a missing value for further analysis.

After the adjustments made for 8MWT and 9HPT as above, SCAFI total score will be calculated as follows:
The mean of the trial1 and trial2 scores are determined for each subtest/hand, and referred to as: 8MW_avg, 9HPT-D_avg, 9HPT-ND_avg and PATA_avg. In case a subtest is only performed once, this value is taken as the mean. Then, the 8MW and 9HPT performance times are converted to the same dimension as the PATA rate, as follows: 8MW_recipr = 1/8MW_avg, 9HPT_recipr = (1/9HPT-D_avg + 1/9HPT-ND_avg)/2. Note that 8MW and 9HPT performance times cannot be 0.
Then each is converted into a Z-score using the following algorithms:

- 8MW_zscore = (8MW_recipr - BL(mean 8MW_recipr)) / BL(SD 8MW_recipr)
- 9HPT_zscore = (9HPT_recipr - BL(mean 9HPT_recipr)) / BL(SD 9HPT_recipr)
- PATA_zscore = (PATA_avg - BL(mean PATA_avg)) / BL(SD PATA_avg)

where BL means baseline value and SD means standard deviation. The mean 8MW_recipr and SD 8MW_recipr are determined using the SAF analysis population.

In case of missing values, the following applies:

- The cases with either 8MW, 9HPT (in one or both hands) or PATA tests not performed at all ("unable to perform due to physical limitations" or "not performed for other reason") are excluded from the calculation of baseline means.
- Only when an 8MW score, 9HPT score or PATA score is missing due to "unable to perform due to physical limitations", then a substitution will be applied as follows (except for baseline values):
  - When 8MW tests were not performed, then 8MW_recipr will be substituted by 1/1800 s.
  - When 9HPT tests were not performed: if only data for one hand is missing, then 9HPT_avg=3000 s for that specific hand; when data for both hands are missing, then 9HPT_recipr=1/3000 s.
  - When PATA tests were not performed, then PATA_avg is substituted with 0.

For agreement on "unable to perform due to physical limitations" or "not performed for other reason", the sponsor will be contacted. The missings created for 8MWT and 9HPT as stated above are considered "unable to perform due to physical limitations".

According to the "SCAFI rating manual", the SCAFI total score is to be determined as the arithmetic mean of the 3 Z-scores. However, following explanation of IntraBio and [redacted], the SCAFI score needs to be calculated as the mean of the non-missing Z-scores. The SCAFI score can only be determined if at least one test is actually performed, i.e. in case all tests were imputed because of missing values, no SCAFI score will be determined. This contradicts the "SCAFI rating manual".

SARA

The overall SARA score is reported as provided in the eCRF. For presentation of the subscore results, the individual results as provided in the eCRF will be used, where for the subscores finger chase, nose-finger test, fast alternating hand movements, heel-shin slide this is the average value for the two sides (left and right) as determined per eCRF.

C-SSRS

Regarding the C-SSRS scores, the following calculations are necessary. The C-SSRS questionnaire collects yes/no responses to 10 categories, as follows:

Suicidal Ideation (1-5)
1 – Wish to be Dead
2 – Non-specific Active Suicidal Thoughts
3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan
5 – Active Suicidal Ideation with Specific Plan and Intent

Suicidal Behavior (6-10)
6 – Preparatory Acts or Behavior
7 – Aborted Attempt
8 – Interrupted Attempt
9 – Actual Attempt (non-fatal)
10 – Completed Suicide

In addition, the following measurement is available as yes/no response: Self-injurious behavior without suicidal intent.

The *Suicidal Ideation Score* is defined as the the maximum suicidal ideation category (1-5 on the C-SSRS) which is responded with 'yes'. Assign a score of 0 if all ideation categories are responded with 'no'.

Composite scores based on the above categories are defined below:

- *Suicidal ideation*: A "yes" answer at any time during treatment to any one of the five suicidal ideation questions (Categories 1-5) on the C-SSRS.

- *Suicidal behavior*: A "yes" answer at any time during treatment to any one of the five suicidal behavior questions (Categories 6-10) on the C-SSRS.

- *Suicidal ideation or behavior*: A "yes" answer at any time during treatment to any one of the ten suicidal ideation and behavior questions (Categories 1-10) on the C-SSRS.

Missing data will not be imputed but will remain missing.

Laboratory

Laboratory safety data measurements that are denoted as smaller/larger than a certain value (e.g. < x.x), will be imputed with this value (e.g. x.x) for calculations of descriptive statistics. Listings will show the value as collected, and a footnote will be added to the summary tables for explanation.

Comments

The following data are either not collected or only collected as free text fields in the eCRF/database, or lack relevant information in the database, and it is therefore necessary that these details are added in the programming code manually. The decisions to drive this manual coding may be documented and finalized during the BDRM but can already be maintained/discussed during the course of the trial for efficiency.

- The reason for video unavailability is recorded as free text field, and it needs to be deducted if any of these reasons consider a "technical issue". The sponsor will provide input.
- PATA score missing due to "unable to perform due to physical limitations" is not available as such in the database but needs to be deducted from a free comment field. The sponsor will provide input.
- Age is not collected during the Extension Phase and full birthdate is not provided in the Parent study; therefore, sponsor will provide details which patients turned 13 between Visit 7 and 8, and between Visit 10 and 11. Note that this may deviate from the age calculations performed for other presentations.
- SCAFI comments as stated above on SCAFI calculations. The sponsor will provide input to which comments relate to "unable to perform due to physical limitations" and which relate to "not performed for other reason".
- Information to match the supplied bottles and/or sachets of study drug with the returned bottles and/or sachets, to be able to differentiate bottles/sachets used for the Parent phase and the Extension phase to allow appropriate compliance calculations.

10.2 Coding

Coding of adverse events, concomitant medication and medical history will be performed by the Data Management provider. Adverse events and medical history are coded with the MedDRA coding system. Concomitant medication is coded according to the WHO drug code and the ATC class code. Coding versions used are documented in the DM documentation. Coding will be supplied as part of the data transfer.

10.3 Analysis software

The statistical analysis and reporting will be done using SAS® for Windows™ version 9.4. SAS tabular output (tables and listings) will be saved in RTF format. SAS graphs will be saved in PNG format. Both will be imported into PDF and/or Word® and supplied to the Medical Writer for use in the clinical study report. When the sponsor wants to receive the output before the study report, then a PDF document is supplied.

10.4 Presentation of tables, listings, graphs

All output will be generated as SAS tables, graphs and listings.

All tables and listings will be created such that they fit landscape pages. The tables for the end-of-text and listings for the appendix will be created using SAS, following the specifications according to the TLF template document that will be created separately.

For graphs, output will be as created as PNG plot. Graphs are created using black, grey and white color only, to facilitate black-and-white printing. Different line patterns and symbols will be used to differentiate between classification or treatment levels. If certain plots can only be visually improved by using colours, then the CMYK colour model will be used instead. Graphs will be created such (i.e. taking into account line thickness and font size) that they can be presented as two (2) per page in the clinical study report.

11 TABLES, LISTINGS, GRAPHS – PARENT PHASE

11.1 General

A detailed list of tables, graphs and listings is presented, if applicable, per report section in sections 11.2, 11.3 and 11.4.
Template tables and listings as well as *example* plots (as received from client or extracted from a relevant paper, if available) will be used as a reference for creation of all output, and a separate document will be created for this. Table/graph/listing numbering will be followed, however, if the data give cause for combining or splitting tables or listings, the numbering may be adapted as necessary. In case there are no data available for a certain table/listing, an empty table will be created and 'No data available' will be stated.

11.2 In-text tables and graphs

Not applicable. Will be designed or extracted by the Medical Writer during creation of the Clinical Study Report, based on the tables and graphs created for section 14 of the CSR.

11.3 End-of-text tables and graphs

Following ICH E3 guidelines, all tables and graphs mentioned here will be presented in Section 14 of the CSR, and tables will be prepared in the order and with section number as stated.

Table/graph number	Contents of table/graph
14.1 Demographic Data Summary figures and tables	
14.1.1-14.1.4	Demographics (ITT, mITT, PPS and FAS population)
14.1.5-14.1.7	Baseline characteristics (ITT, mITT and PPS population)
14.1.8	Disposition
14.1.9	Medical history
14.1.10	A-T specific history
14.1.11	Compliance
14.2 Efficacy Data Summary figures and Tables	
14.2.1	Result of t-test or Wilcoxon test on the primary endpoint (mITT and PPS), including sensitivity analysis (only mITT).
14.2.2	Frequency table of the CI-CS score Visit 4 vs Visit 2 minus the CI-CS score Visit 6 vs Visit 4, combined with the frequency table of the CI-CS score Visit 4 vs Visit 2 and separately, the CI-CS score Visit 6 vs Visit 4 (mITT and PPS population)
14.2.3	Descriptive statistics of the CI-CS score Visit 4 vs Visit 2 minus the CI-CS score Visit 6 vs Visit 4, combined with the descriptive statistics of the CI-CS

	score Visit 4 vs Visit 2 and separately, the CI-CS score Visit 6 vs Visit 4 (mITT and PPS population).
14.2.4	Bar chart of CI-CS score Visit 4 vs Visit 2 minus CI-CS score Visit 6 vs Visit 4 (mITT and PPS population)
14.2.5	Frequency table of the CI-CS score Visit 4 vs Visit 2 minus the CI-CS score Visit 6 vs Visit 4 according to subgroups, combined with the frequency table of the CI-CS score Visit 4 vs Visit 2 and separately, the CI-CS score Visit 6 vs Visit 4 according to subgroups (mITT population)
14.2.6	Descriptive statistics of the CI-CS score Visit 4 vs Visit 2 minus the CI-CS score Visit 6 vs Visit 4 according to subgroups, combined with the descriptive statistics of the CI-CS score Visit 4 vs Visit 2 and separately, the CI-CS score Visit 6 vs Visit 4 according to subgroups (mITT population)
14.2.7	Bar chart of CI-CS score Visit 4 vs Visit 2 and separately, CI-CS score Visit 6 vs Visit 4 (mITT and PPS population)
14.2.8	ICC analysis (mITT population)
14.2.9	Result of t-test or Wilcoxon test on the key secondary endpoint 'Change in severity score based on averaged CI-S' (mITT and PPS),
14.2.10	Frequency table of the change in severity score based on averaged CI-S scores between baseline and treatment minus the change between treatment and washout (mITT and PPS population)
14.2.11	Descriptive statistics of the change in severity score based on averaged CI-S scores between baseline and treatment minus the change between treatment and washout (mITT and PPS population)
14.2.12	Bar chart of change in severity score based on averaged CI-S scores between baseline and treatment minus the change between treatment and washout (mITT and PPS population)
14.2.13	Frequency table of the change in severity score based on averaged CI-S scores between baseline and treatment minus the change between treatment and washout according to subgroups (mITT population)
14.2.14	Descriptive statistics of change in severity score based on averaged CI-S scores between baseline and treatment minus the change between treatment and washout according to subgroups (mITT population)
14.2.15	Result of Wilcoxon test on the key secondary endpoint 'CI-CS score reclassified' (mITT and PPS)
14.2.16	Frequency table of the CI-CS score reclassified on a 3-point scale Visit 4 vs Visit 2 and separately, the reclassified CI-CS score Visit 6 vs Visit 4 (mITT and PPS population)
14.2.17	Descriptive statistics of the CI-CS score reclassified on a 3-point scale Visit 4 vs Visit 2 and separately, the reclassified CI-CS score Visit 6 vs Visit 4 (mITT and PPS population)
14.2.18	Bar chart of CI-CS score reclassified on a 3-point scale Visit 4 vs Visit 2 and separately, CI-CS score Visit 6 vs Visit 4 (mITT and PPS population)

14.2.10	Frequency table of the CI-CS score reclassified on a 3-point scale Visit 4 vs Visit 2 and separately, the reclassified CI-CS score Visit 6 vs Visit 4 according to subgroups (mITT population)
14.2.20	Descriptive statistics of the CI-CS score reclassified on a 3-point scale Visit 4 vs Visit 2 and separately, the reclassified CI-CS score Visit 6 vs Visit 4 according to subgroups (mITT population)
14.2.21	Frequency table of the CI-CS score for the non-primary anchor test Visit 4 vs Visit 2 and separately, the CI-CS score Visit 6 vs Visit 4 (mITT and PPS population)
14.2.22	Descriptive statistics of the CI-CS score for the non-primary anchor test Visit 4 vs Visit 2 and separately, the CI-CS score Visit 6 vs Visit 4 (mITT and PPS population)
14.2.23	Frequency table of the CI-CS score for the non-primary anchor test Visit 4 vs Visit 2 and separately, the CI-CS score Visit 6 vs Visit 4 according to subgroups (mITT population)
14.2.24	Descriptive statistics of the CI-CS score for the non-primary anchor test Visit 4 vs Visit 2 and separately, the CI-CS score Visit 6 vs Visit 4 according to subgroups (mITT population)
14.2.25	Result of t-test or Wilcoxon test on the change in SARA total score between Visit 2 and Visit 4, as well as Visit 4 and Visit 6 (mITT and PPS)
14.2.26	Descriptive statistics of the SARA total score and 8 subscores at each visit (mITT and PPS population)
14.2.27	Mean or median plot versus time of the SARA total score (mITT and PPS population)
14.2.28	Stacked bar chart of the 8 SARA subscores at each visit (mITT and PPS population)
14.2.29	Spaghetti plot of SARA total score and 8 subscores at each visit (mITT and PPS population)
14.2.30	Descriptive statistics of the SARA total score and 8 subscores at each visit according to subgroups (mITT population)
14.2.31	Result of t-test or Wilcoxon test on the change in SCAFI total score, and subscores 8MW_avg, 9HPT-D_avg and PATA_avg between Visit 2 and Visit 4, as well as Visit 4 and Visit 6 (mITT and PPS)
14.2.32	Descriptive statistics of the SCAFI total score and subscores 8MW_avg, 9HPT-D_avg, 9HPT-ND_avg and PATA_avg at each visit (mITT and PPS population)
14.2.33	Mean or median plot of SCAFI total score versus time (mITT and PPS population)
14.2.34	Spaghetti plot of SCAFI total score versus time (mITT and PPS population)
14.2.35	Descriptive statistics of the SCAFI total score and subscores 8MW_avg, 9HPT-D_avg, 9HPT-ND_avg and PATA_avg at each visit according to subgroups (mITT population)

14.2.36	Frequency table of the EQ-5D-5L and EQ-5D-Y health status and 5 subdomains at each visit (mITT and PPS population)
14.2.37	Frequency table of the EQ-5D-5L and EQ-5D-Y health status and 5 subdomains at each visit according to subgroups (mITT population)
14.2.38	Descriptive statistics of the EQ-VAS for -5L and -Y at each visit (mITT and PPS population)
14.2.39	Mean or median plot of EQ-VAS versus time, for -5L and -Y separately (mITT and PPS population)
14.2.40	Spaghetti plot of EQ-VAS versus time, for -5L and -Y separately (mITT and PPS population)
14.2.41	Descriptive statistics of the EQ-VAS for -5L and -Y at each visit according to subgroups (mITT population)
14.2.42	Frequency table of the 3 CGI-S scores (treating physician, caregiver and patient) at each visit (mITT and PPS population)
14.2.43	Descriptive statistics of the 3 CGI-S scores (treating physician, caregiver and patient) at each visit (mITT and PPS population)
14.2.44	Bar charts of the 3 CGI-S scores (treating physician, caregiver and patient) at each visit (mITT and PPS population)
14.2.45	Mean or median plot versus time of the 3 CGI-S scores (treating physician, caregiver and patient) (mITT and PPS population)
14.2.46	Spaghetti plot of the 3 CGI-S scores (treating physician, caregiver and patient) versus time (mITT and PPS population)
14.2.47	Frequency table of the 3 CGI-S scores (treating physician, caregiver and patient) at each visit according to subgroups (mITT population)
14.2.48	Descriptive statistics of the 3 CGI-S scores (treating physician, caregiver and patient) at each visit according to subgroups (mITT population)
14.2.49	Frequency table of the change of the 3 CGI-C scores (treating physician, caregiver and patient) between Visit 2 vs Visit 4, and between Visit 4 and Visit 6 (mITT and PPS population)
14.2.50	Descriptive statistics of the change of the 3 CGI-C scores (treating physician, caregiver and patient) between Visit 2 vs Visit 4, and between Visit 4 and Visit 6 (mITT and PPS population)
14.2.51	Bar charts of the 3 CGI-C scores (treating physician, caregiver and patient) between Visit 2 vs Visit 4, and between Visit 4 and Visit 6 (mITT and PPS population)
14.2.52	Frequency table of the change of the 3 CGI-C scores (treating physician, caregiver and patient) between Visit 2 vs Visit 4, and between Visit 4 and Visit 6 according to subgroups (mITT population)
14.2.53	Descriptive statistics of the change of the 3 CGI-C scores (treating physician, caregiver and patient) between Visit 2 vs Visit 4, and between Visit 4 and Visit 6 according to subgroups (mITT population)

14.2.54	Forest plots
14.3 Safety Data Summary figures and tables – 14.3.1 Displays of Adverse Events	
14.3.1.1	Overview adverse events
14.3.1.2	Treatment emergent adverse events
14.3.1.3	Treatment emergent adverse events by severity grade
14.3.1.4	Treatment emergent adverse events by relationship
14.3.1.5	Treatment emergent adverse events leading to premature discontinuation
14.3 Safety Data Summary figures and tables – 14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events	
14.3.2.1	SAEs
14.3.2.2	Deaths
14.3 Safety Data Summary figures and tables – 14.3.4 Abnormal Laboratory Value Listing (each patient)	
14.3.4.1	Out of range clinical laboratory listing
14.3.4.2	Clinical laboratory – haematology
14.3.4.3	Clinical laboratory – clinical chemistry
14.3.4.4	Clinical laboratory – urinalysis
14.3.5	Vital signs
14.3.6	Orthostatic blood pressure
14.3.7	ECG
14.2.8	C-SSRS
14.3.9	Prior and concomitant medication and therapies

11.4 Listings

Following ICH E3 guidelines, all listings mentioned here will be presented in Section 16.2 of the CSR, and listings will be prepared in the order and with section number as stated.

Individual listings will be prepared of the data collected in the database, following CDISC data format. No combining of data other than mentioned in this paragraph will be performed. The key variables in the listings (except for a few displaying screening data) will be patient number, and age/weight/dosing group. If applicable, visit number will be listed additionally. Furthermore, a listing containing study visit dates will be presented.

Listing number	Contents of listing
16.2.1 Discontinued patients	
16.2.1.1	Inclusion/exclusion criteria – deviations
16.2.1.2	Patient disposition
16.2.2 Protocol deviations	
16.2.2	Protocol deviations
16.2.3 Demographic and baseline data	
16.2.3.1	Demographics
16.2.3.2	Baseline characteristics
16.2.3.3	Medical history
16.2.3.4	A-T specific history
16.2.4 Compliance and/or treatment data	
16.2.4.1	Drug administration
16.2.4.2	Drug accountability
16.2.4.3	Study visits
16.2.5 Individual efficacy response data	
16.2.5.1	Individual CI-S and CI-CS scores
16.2.5.2	Individual scores on ataxia and functioning - SARA test
16.2.5.3	Individual scores on ataxia and functioning - SCAFI test
16.2.5.4	Individual health related quality of life – EQ-5D-5L, EQ-5D-Y and the respective EQ-VAS
16.2.5.5	Individual global impression scores – CGI-S
16.2.5.6	Individual change in global impression scores – CGI-C
16.2.6 Adverse event listings	
16.2.6.1	Adverse events
16.2.6.2	SAEs
16.2.6.3	Deaths

16.2.6.4	AEs leading to discontinuation from the study
16.2.6.5	Vital signs, including orthostatic
16.2.6.6	ECG
16.2.6.7	C-SSRS
16.2.6.8	Physical examination
16.2.6.9	Prior and concomitant medication and therapy
16.2.7 Listing of individual laboratory measurements by patient	
16.2.7.1	Laboratory safety data – haematology
16.2.7.2	Laboratory safety data – clinical chemistry
16.2.7.3	Laboratory safety/pregnancy data – urinalysis
16.2.7.4	General comments

12 TABLES, LISTINGS, GRAPHS – EXTENSION PHASE

12.1 General

A detailed list of tables, graphs and listings is presented, if applicable, per report section in Sections 12.2, 12.3 and 12.4.
Template tables and listings as well as *example* plots (as received from client, a previous study, or extracted from a relevant paper, if available) will be used as a reference for creation of all output, and a separate document will be created for this. Table/graph/listing numbering will be followed, however, if the data give cause for combining or splitting tables or listings, the numbering may be adapted as necessary. In case there are no data available for a certain table/listing, an empty table will be created and 'No data available' will be stated.

12.2 In-text tables and graphs

Not applicable. Will be designed or extracted by the Medical Writer during creation of the Clinical Study Report, based on the tables and graphs created for Section 14 of the CSR.

12.3 End-of-text tables and graphs

Following ICH E3 guidelines, all tables and graphs mentioned here will be presented in Section 14 of the CSR, and tables will be prepared in the order and with section number as stated.

Table/graph number	**Contents of table/graph**
14.1 Demographic Data Summary figures and tables	
14.1.12-14.1.13	Demographics (mITTe and SAFe)

14.1.14-14.1.15	Baseline characteristics (mITTe)
14.1.16	Disposition
14.1.17	Medical history
14.1.18	A-T specific history
14.1.19	Compliance
14.2 Efficacy Data Summary figures and Tables	
14.2.55	SARA total score statistical analysis (mITTe)
14.2.56	SARA total score success rates (mITTe)
14.2.57	SARA total score success rates per subgroup (mITTe)
14.2.58	Descriptive statistics of the SARA total score at each visit, including change values between visits (mITTe)
14.2.59	Descriptive statistics of the SCAFI total score and subscores 8MW_avg, 9HPT-D_avg, 9HPT-ND_avg and PATA_avg at each visit, including change values between visits (mITTe)
14.2.60	Frequency table of the EQ-5D-5L and EQ-5D-Y health status and 5 subdomains at each visit (mITTe)
14.2.61	Descriptive statistics of the EQ-VAS for -5L and -Y combined at each visit (mITTe)
14.2.62	Frequency table of the 3 CGI-S scores (treating physician, caregiver and patient) at each visit (mITTe)
14.2.63	Descriptive statistics of the 3 CGI-S scores (treating physician, caregiver and patient) at each visit (mITTe)
14.2.64	Frequency table of the 3 CGI-C scores (treating physician, caregiver, and patient) at each visit (mITTe)
14.2.65	Descriptive statistics of the 3 CGI-C scores (treating physician, caregiver, and patient) at each visit (mITTe)
14.3 Safety Data Summary figures and tables – 14.3.1 Displays of Adverse Events	
14.3.1.10	Overview adverse events
14.3.1.11	Treatment emergent adverse events
14.3.1.12	Treatment emergent adverse events by severity grade
14.3.1.13	Treatment emergent adverse events by relationship
14.3.1.14	Treatment emergent adverse events leading to premature discontinuation
14.3.1.15	Treatment emergent adverse events by treatment cycle

14.3.1.16	Treatment emergent adverse events by severity grade by treatment cycle
14.3.1.17	Treatment emergent adverse events by relationship by treatment cycle
14.3.1.18	Treatment emergent adverse events leading to premature discontinuation by treatment cycle
14.3 Safety Data Summary figures and tables – 14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events	
14.3.2.3	SAEs
14.3.2.4	Deaths
14.3 Safety Data Summary figures and tables – 14.3.4 Abnormal Laboratory Value Listing (each patient)	
14.3.4.5	Out of range clinical laboratory listing
14.3.4.6	Clinical laboratory – haematology
14.3.4.7	Clinical laboratory – clinical chemistry
14.3.4.8	Clinical laboratory – urinalysis
14.3.10	Vital signs
14.3.11	ECG
14.2.12	C-SSRS
14.3.13	Prior and concomitant medication and therapies
14.3.14	Physical examination

12.4 Listings

Following ICH E3 guidelines, all listings mentioned here will be presented in Section 16.2 of the CSR, and listings will be prepared in the order and with section number as stated.

Individual listings will be prepared of the data collected in the database, following CDISC data format. No combining of data other than mentioned in this paragraph will be performed. The key variables in the listings (except for a few displaying screening data) will be patient number, and age/weight/dosing group. If applicable, visit number will be listed additionally. Furthermore, a listing containing study visit dates will be presented.

16.2.3 Demographic and baseline data	
16.2.3.5	Demographics
16.2.3.6	Baseline characteristics

16.2.3.7	Medical history
16.2.3.8	A-T specific history
16.2.4 Compliance and/or treatment data	
16.2.4.4	Drug administration
16.2.4.5	Drug accountability
16.2.4.6	Study visits
16.2.5 Individual efficacy response data	
16.2.5.7	Individual scores on ataxia and functioning - SARA test
16.2.5.8	Individual scores on ataxia and functioning - SCAFI test
16.2.5.9	Individual health related quality of life – EQ-5D-5L, EQ-5D-Y and the respective EQ-VAS
16.2.5.10	Individual global impression scores – CGI-S (treating physician, caregiver, and patient)
16.2.5.11	Individual change in global impression scores – CGI-C (treating physician, caregiver, and patient)
16.2.6 Adverse event listings	
16.2.6.6	Adverse events
16.2.6.7	AEs leading to discontinuation from the study
16.2.6.8	Vital signs
16.2.6.9	ECG
16.2.6.10	Prior and concomitant medication and therapies
16.2.6.11	Physical examination
16.2.7 Listing of individual laboratory measurements by patient	
16.2.7.7	Laboratory safety data – haematology
16.2.7.8	Laboratory safety data – clinical chemistry
16.2.7.9	Laboratory safety/pregnancy data – urinalysis
16.2.7.10	Listing of urine test for N-Acetyl-D-Leucine
16.2.7.11	Listing of PK concentration data
16.2.7.12	General comments